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THOMAS LEWIS

Thomas Lewis was born at Cardiff on December 26, 1881. His father and mother, who were both Welsh, took a great interest in the education of their children and to this Lewis attributed his later success as a scientist. Except for one year at Clifton College, Lewis, up to the age of sixteen years, was educated entirely at home. He took little interest in book learning during these years, preferring to spend his time in the country, satisfying his innate curiosity in respect of natural objects, and his interest in outdoor sports. Before he was ten years old he had decided to become a doctor, but he apparently failed to realize the educational implications of this decision, for he failed in his London matriculation examination when he was sixteen. This failure, as one would expect, did not deter him, but goaded him to apply himself to his books.

A year later he matriculated in the first division in the University of London and never failed in any subsequent examination. A brilliant student career followed, first at Cardiff and later at University College Hospital, London. In 1905 he qualified as M.B., B.S. (London), winning a triple distinction and the University Gold Medal, and gained the D.Sc., Wales. During this time he had already shown his interest in research, for, with Swale Vincent at Cardiff, he had published a series of papers on the proteins of unstriped muscle and on the hæmolymph glands. As a student at University College Hospital he carried out some researches but stated that he achieved nothing. He was, however, meeting men of great ability such as Dale and Elliott and Noon of the Physiological Society, lunching with seniors like Starling, Bayliss, and Cushing, and it was quite clear that his interest was steadily moving in the direction of a research life.

He started work, in fact, in Starling's physiological laboratory in 1907; but in 1909 he put up his plate in Wimpole Street. This action, which suggested that he could not make up his mind whether to take up a research career or a consultant's life, was determined by the fact that opportunities for full-time research were practically non-existent to a man without private means. Lewis, though the son of a well-to-do father, was not the man to rely on parental wealth.

In 1908 Lewis met James Mackenzie. He was stirred by Mackenzie's critical attitude to medicine, and his independence of authority, under the spell of which he had fallen while in hospital. Mackenzie had a profound influence, for not only did he urge Lewis to take up research but suggested a problem, namely, the analysis of irregular cardiac actions. Lewis quickly saw that the string galvanometer, which Einthoven had recently developed, was the instrument most likely to give results in this field, and started his researches, both in the laboratory and the clinic, which added so much knowledge to the subject. Even at this stage his careful nature did not allow him completely to take the chances of a research life, so he combined hospital work and private practice with his research work. In 1910 he obtained the first of the newly created Beit Memorial Fellowships, but he did not relinquish private practice until 1916, when he was appointed a physician on the staff of the Medical Research Committee, as the Medical Research Council was then called.

He was then able to throw all his energies into research, as he had long wished to do. Even during the transitional period he achieved more than most would have done, had they given their full time to research. He published in 1911 his first book, *The Mechanism of the Heart Beat*, a book written for advanced students which gained in size as new knowledge, mainly from his own laboratory, was obtained, and became the " bible " of all those interested in cardiographic work. About the same time he also published two small books, namely *Clinical Disorders of the Heart Beat* (1912) and *Clinical Electrocardiography* (1913), which were written for practitioners. The character of these two books clearly indicates what Lewis always kept in mind: to seek for new knowledge and to use it for the simplification of diagnosis

and treatment of the sick. In addition, not satisfied with the opportunities for publishing the scientific data of his work, he founded in 1909 (with Mackenzie's help) and edited a new journal, *Heart*.

In 1916, when Lewis was only 33 years old, he published a series of remarkable papers in the Philosophical Transactions of the Royal Society; they detailed with remarkable clarity the spread of the electrical process across the chambers of the heart, when it was beating normally and abnormally, and related the findings to normal and abnormal human electrocardiograms. These papers are models of publication, not only in the clearness of presentation but also in the beauty of the illustrations, all of which he prepared himself. (Of this mass of work, that relating to the electrocardiogram of right and left bundle branch block has alone failed to stand the test of time.) This work was outlined in his Croonian Lecture to the Royal Society in 1917, and he was elected a Fellow in 1918.

During the First World War, Lewis was asked to investigate the condition known as "Soldier's heart" (D.A.H.) which was causing a serious loss of man power in the Army. With Meakins and Parkinson he directed the clinical services of a special hospital for this purpose, first at Hampstead and later at Colchester. With his characteristic energy he tackled his new problems and defined the condition, which he renamed "effort syndrome," and devised a treatment of graduated exercises which was eminently successful. As consulting physician to the Ministry of Pensions he took the opportunity of keeping in touch with a large number of soldiers pensioned with heart trouble for a sufficient length of time to gain further knowledge of the diagnosis, prognosis, and treatment of patients suffering from real or suspected cardiac disease. He also published a paper on dermatographism presenting the evidence for the independent contractile power of the capillaries. He received the C.B.E. in 1920 and a year later was knighted for his work during the war and for the Ministry of Pensions.

The war over, Lewis took up the study of the mechanism underlying auricular flutter and fibrillation. By a series of interrelated experiments on dogs and human beings, he concluded that the mechanism was that of a wave circulating around the mouths of the great veins. It was in his view a "circus movement" similar to that already described in cold-blooded contractile tissues. This conception has been generally accepted, though some workers could not unreservedly accept it.

When he was about 43 years old, the character of his researches underwent a striking change. He had decided that the proper subject to study was man, and henceforward he worked with man almost to the exclusion of animals. He gave up the complex technique of electrocardiography, involving animals, and turned to problems in man, using simpler techniques. He took up problems that had interested him during the war and studied the reaction of the skin vessels to injury. He obtained evidence that with all forms of injury a substance, "H substance," was liberated, which was indistinguishable from histamine, but which he refrained from calling histamine, as conclusive evidence was lacking. All this work he published in his book *Blood Vessels of the Human Skin*.

In 1927 he was awarded a Royal Medal by the Royal Society. In the same year work was interrupted by his first attack of coronary thrombosis; unacquainted with the recent American work on this subject he did not at first recognize the nature or the seriousness of his illness. It was with difficulty that he accepted the need for prolonged rest. The pain he suffered was intense, and this stimulated his later interest in this subject. He made an excellent recovery, but, recognizing the need for less strain he moved to the country, choosing gardening and fishing as recreations. He again set to work and continued his observations upon peripheral blood vessels, and showed that the pain of intermittent claudication was due to a chemical and physico-chemical stimulus which he called factor P: it was not identified. Evidence was also obtained which suggested that the pain of angina was due to a similar mechanism. Further work on skin tenderness led to Lewis postulating the existence of a new system of nerves which were called by him "nocifensor nerves." These researches were published in book form (*Pain*) in 1942. In 1941 Lewis was awarded the Copley Medal of the Royal Society and in 1945 the Conway Evans Prize.

In addition to the study of specially selected patients, Lewis continued to see hospital patients suffering from all kinds of cardiovascular diseases. As a result of this he published two

more books, *Diseases of the Heart* in 1933 and *Vascular Disorders of the Limbs* in 1937. They were designed for clinical use and contained much that was new.

All this time Lewis had been considering how he could foster and perpetuate such work as he was successfully accomplishing. He set himself to attract young men to his way of life and thinking, and published two books, *Clinical Science, Illustrated by Personal Experience* (1934) and *Research in Medicine and other Addresses* (1938) which gave expression to his creed. He ensured that opportunities were available for those wishing to carry out clinical research, by scholarships, grants, and by the establishment in other hospitals of departments like his own. In 1937 the financial support of his appointment was transferred to a Trust endowed by the Rockefeller Foundation. At the same time, he founded the Medical Research Society as a meeting ground for critical discussion and the promotion of friendship among those engaged in clinical research, and was its first chairman. He maintained a close contact with the Cardiac Club which was founded in 1922; and was Chairman at its first meeting in London that year. He had agreed to be chairman at the annual meeting of its successor the Cardiac Society in 1945, but wrote some little time before his death regretting that he would not be well enough to do so. When the Cardiac Society decided to start the *British Heart Journal* in 1939 they were pleased to have a Foreword written by him as a welcome start. In 1933 he had changed the title of his journal *Heart* to that of *Clinical Science* and passed the control of the journal into the hands of the Medical Research Society in 1938, though he remained editor till 1944.

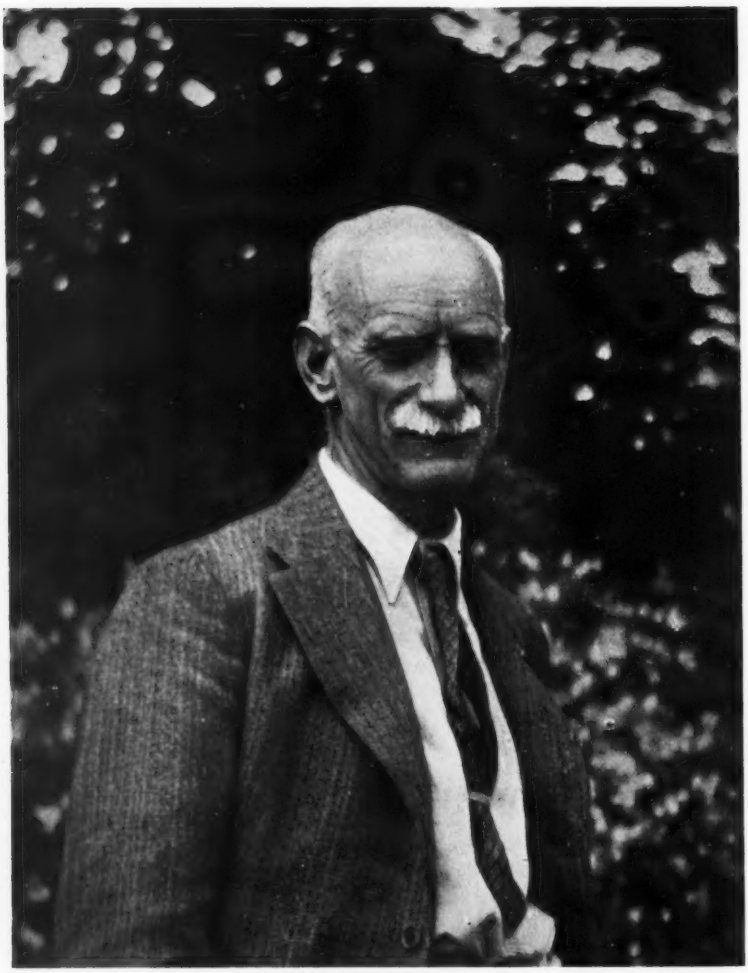
When the Second World War broke out he tried to pursue research in relation to war needs, but could not find an opportunity. He therefore took on more teaching to free others, and carried on with his researches, but towards the end of 1944 his health broke down again (he had had a second attack of coronary thrombosis in 1935), and he died in the spring of 1945. He was buried at Llangorst Church, Llangasty, Brecon.

In such a small compass it is not possible to give more than the barest outline of his achievements. He published about 230 papers in all and wrote 12 books. He disciplined himself to write in a clear and concise style and in later life could write swiftly and without amendment. He took the greatest care in his writings to present all the evidence, not wishing that anything should be accepted on his authority alone. As an editor he insisted on a very high standard from all his contributors. Many received their manuscripts back for revision with some dismay at the number of pencilled alterations. Those who went through them personally with him had a trying ordeal. Some complained that the individuality of the author became lost but most recognized the great improvement that came from his criticisms.

As a teacher he had the faculty of making difficult subjects clear and interesting. He always developed his story in a simple and logical manner and tried to instil into his students the power of observation and reasoning. He was interested in medical education and as late as last year he published an article in the *Lancet* outlining his views.

To cardiologists he will chiefly be remembered during the years up to 1935. He was not an impressive figure in those early days. He was of medium height, spare built, active and tireless. Two characteristics arrested attention, the penetrating look of his deep blue eyes and his quiet voice. He was then in full health, working with unremitting energy year after year, for ten months on end. Problem after problem was attacked in the laboratory, information continually collected in the clinic, which gave knowledge not only to the advanced student but to those dealing with the diagnosis, prognosis, and treatment of cardiac disease. He grudged every minute not spent on his actual problems. Public holidays, committees, discussions on general scientific problems, small talk, were all disregarded if he felt they interfered with the speed of his work. He was capable of driving himself at high pressure and expected the same of his co-workers. They found the pace terrific, and knew there could be no respite till the specific problem in hand was solved or he went away for his annual holiday. Then, for two months on end, he gave the same energy and enthusiasm to watching and photographing birds. In this, as in many other aspects of his life, he received much help and encouragement from his wife (whom he married in 1916); and many will remember the beautiful photographs they saw when they visited him in his delightful home.

To work with him revealed his great characteristics, which were not always evident to those who knew him slightly. A man of contrasts, he was difficult to know well and difficult



THOMAS LEWIS

to understand. He was a humble-minded man, entirely honest, and ready to give help to all those who sincerely asked for it, and able to talk freely on many scientific subjects. He was at the same time a man of great reserve and singleness of purpose. In consequence, when he was immersed in a problem, his impatience, hardness, hatred of slipshod work, and his outspoken manner were not understood by those who did not appreciate his way of life; a sense of ruthlessness was in his work. He resented ill-formed criticism, and defended his views vigorously, but when he was convinced that proper evidence had been brought forward from the newer view, he accepted it without question, for he venerated the truth. He not only won universal admiration for his scientific achievements, but all his associates had a great personal regard for him.

In 1929 thirty-seven of his colleagues (all who had worked with him at University College up to that date) gave him a volume of their photographs and in a letter expressed their thanks for his help by teaching and example and for his many acts of kindness. This gift, arising as a spontaneous expression of their high regard for him, gave him great pleasure. Had this gift been delayed till much later, and had it been possible to include all those who had benefited by his example and teaching, it would have been an immense volume. It has fallen to few scientists to achieve so much and to have had such a profound influence upon the subjects which they have fostered.

A. N. DRURY
R. T. GRANT

Lewis can scarcely be regarded as a pupil of Mackenzie; rather he was already trained, scientifically mature, and well fitted to extend and consolidate the modern conception of cardiac disease which began in Britain early this century. Let us say that Mackenzie was passionately dissatisfied with what he could tell and what he could do for his patients, and so he bent his powerful mind to research mostly by observation. He recognized the calibre of Lewis and persuaded him that here was the opportunity for his talent. Observation was not enough, planned scientific experiment was essential, the electrocardiograph was available, and Lewis started on his course. In no hurry, patiently and steadfastly, he forgot himself in this great work on cardiac physiology, animal and human. I like to think it was Mackenzie, a practitioner of medicine, who coloured the physiology of Lewis to a human tint. However that may be, Lewis was not to be confined to the laboratory, but went to the out-patient department and the wards. He felt it natural that the scientific method should be applied to research in practical medicine, that medicine itself should be directed and developed by clinical science.

Thinkers are not common, and when a thinker is also a doer you have a rare combination. Meeting Lewis was not always easy, though later it became easier. His modesty could not hide the fact that he was indeed superior—a superman of a wholesome kind. He had a reserved manner in social contact, suggesting that his energy was concentrated so much on his life's work that little interest remained for casual visitors or acquaintances. With closer contact, however, anyone showing real interest and a willingness to be corrected, would not fail to receive help and encouragement. His standards were set high, personally and editorially. Did he not once reject for *Heart* a paper from Mackenzie, who took it in good part after the first shock?

As a writer of precise and lucid English, carefully adapted to scientific work, Lewis was also distinguished. He had something to explain or to tell, and he left no doubt as to his meaning. More remarkable is the fact that one man could so combine physiological knowledge with a grasp of the essentials of medical teaching and practice. His brief *Diseases of the Heart* is sufficient proof of this blend of scientist and clinician.

Our feeling about Sir Thomas Lewis might be expressed as gratitude and pride that we have had with us so great and so good a man who dedicated himself to the service of humanity, and chose the field of cardiology and of clinical science.

JOHN PARKINSON

THE MECHANISM OF THE WENCKEBACH TYPE OF A-V BLOCK

BY

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The Wenckebach type of auriculo-ventricular block is characterized by a progressive lengthening of the A-V conduction time, ending in a completely blocked auricular complex—the Wenckebach period. These periodically recurring dropped beats were first recognized clinically by Wenckebach in 1899 from a careful analysis of radial arteriograms; Engelmann (1896) had noted the same phenomenon in the frog's heart a few years earlier. Changing conduction times, due to varying degrees of recovery of the A-V junction, were postulated by them to account for the dropped beats. A typical feature of the progressive prolongation of the P–R interval is that the most marked increase in the conduction time is seen in the second complex of the group. Later ones show only slightly greater prolongation. The shortest A-V conduction time is seen in the first complex after the dropped beat; i.e. following the longest pause or the longest R–P interval.

Clinically, the Wenckebach type of A-V block is seen especially in digitalis poisoning, in infective myocarditis, due particularly to rheumatic fever and diphtheria, in myocardial fibrosis or infarction due to coronary artery disease, and occasionally in other lesions of the conduction system. It occurs at low auricular rates, most often under the influence of digitalis, or at the high auricular rates of paroxysmal tachycardia (Wenckebach and Winterberg, 1927; Decherd, *et al.*, 1943). A-V block, often of the Wenckebach type, has been produced experimentally by increasing the auricular rate (von Kries, 1902; Erlanger, 1906; Lewis, White, and Meakins, 1913; Lewis and Master, 1925; Ashman, 1925), by vagus stimulation (Mines, 1914; Lewis, 1925; Rothberger, 1931), by cold (Ganter and Zahn, 1912), by pressure (Gaskell, 1882; Erlanger and Blackman, 1909), by ischæmia (Engelmann, 1896), by asphyxia (Lewis and Mathison, 1910; Lewis, White, and Meakins, 1913), by acidosis (Mines, 1913), by various glucosides (W. Straub, 1901; Alcock and Meyer, 1903), by vagomimetic drugs (Starr, 1936; Decherd and Ruskin, 1943), by auricular ectopic beats (Erlanger, 1906; Rothberger 1931; Zeisler, 1931; Schellong, 1931) and by interpolated ventricular ectopic beats (de Boer, 1915; H. Straub, 1918).

The intimate cellular processes that underlie conduction of myocardial excitation are at present obscure; the same obscurity of the fundamental mechanisms involved applies to defective conduction or heart block. The simple physiological properties of excitability, conductivity, refractoriness, and the like are, however, susceptible to study, and it is in such terms that the problems associated with complete or incomplete conduction must be discussed.

Various explanations of Wenckebach periods, which Wenckebach (1899) himself compared to the Luciani periods of rhythmicity of the markedly depressed heart, have been proposed from time to time. W. Straub (1901) produced Wenckebach periods and 2 : 1 A-V block in the isolated frog heart by means of antiarin, and likewise explained these phenomena in terms of decreased excitability or increased refractoriness of the ventricle to regular stimuli. Von Kries (1902) produced Wenckebach periods and 2 : 1 A-V block by warming the auricle and cooling the ventricle, and explained them in terms of the arrival of auricular stimuli earlier and earlier in ventricular diastole and the ventricular refractory

period, thus interfering with ventricular recovery. Trendelenburg (1903) produced Wenckebach periods in ventricular muscle strips, presumably lacking specialized conduction fibres, by increasing the frequency of electrical stimulation, and felt that variable latency was responsible for the block, not diminished conductivity. Hering (1904) invoked the diastolic recovery of reactivity, or Reaktionsbereitschaft, of the ventricular muscle, linking in this term the myocardial properties of irritability, conductivity, and contractility. A rise in auricular rate, diminution of ventricular excitability, or a fall in stimulus strength could, in his opinion, delay the recovery of the ventricular muscle and increase its refractory phase to auricular stimuli, with the production of dropped beats.

The idea of ventricular latency elaborated by Erlanger (1906, 1912), had to be abandoned when Hering (1910) and later workers (Lewis, White, and Meakins, 1913; Lewis and Master, 1925) localized the delay in A-V conduction within the A-V node, probably at the junction of its auricular and ventricular components (Kung and Mobitz, 1930). Mobitz (1924) centered the latency, which he related to the refractory phase of electrical excitability, in the A-V node. Variable A-V conductivity, in his opinion, resulted from variable A-V nodal latency, since he found the difference between maximum and minimum latency was greater than A-V conduction time, and felt, contrary to Lewis (1912), that all parts of the heart conducted at the same rate. He also based his conclusions upon a cryptic interpretation of two types of recovery curves. Gilson (1942) has lately proposed an " excitation time " theory of A-V delay to take the place of the latency theory.

Mobitz' more important contribution was the first recovery curve of conductivity, drawn from an electrocardiogram with a varying auricular rate, showing the reciprocal relation of P–R to the preceding R–P intervals. From the logarithmic curve, which our curves closely resemble, he pointed out that recovery is fastest in the earliest portion of the relative refractory period, and slowest at the end.

Schellong (1924) published a series of experiments on normal and digitalized ventricular strips of the frog heart, which were partially divided or pressed into a bridge simulating the A-V junction. He drew recovery curves of excitability, which closely resembled those of stimulus propagation (Erregungsfortpflanzung), thus linking the properties of conductivity and excitability. Whereas rhythmical stimulation of normal muscle strips caused no decrease in excitability, so that all stimuli were conducted, similar stimulation of digitalized strips resulted in partial block with Wenckebach periods. He concluded that digitalis delayed the recovery of excitability, so that successive stimuli fell earlier and earlier in the relative refractory period, resulting finally in a dropped beat. He postulated, therefore, that frequency of stimulation and the presence of a relative refractory period were the two factors underlying the Wenckebach type of block. He also pointed out that the period of electrical latency was less than 0·002–0·004 sec.; furthermore, that the latency between the auricle and the A-V node was measurable only when the stimulus was minimal, whereas the physiological stimuli were actually four to five times the threshold strength.

Samoiloff (1929) has attempted to explain the production of the Wenckebach type of block in ventricular bridges in terms of gradual prolongation of the absolute and relative refractory periods. Lewis and Master (1925) have demonstrated the lengthening of the refractory periods of the A-V tissues with slower auricular rates, and on this basis, and the shorter preceding recovery period, explained the maximum prolongation of the P–R interval in the second conducted beat of the Wenckebach period. Ashman (1925) plotted curves of recovery of conductivity in turtle heart muscle compressed at the A-V junction. The longer the interval between break shocks to the auricle, the shorter was the A-V interval. The latter increased as the rest period between stimuli became shorter than that permitting complete recovery, and finally 2 : 1 A-V block resulted. Whether this point was the absolute refractory period of conductivity or represented a certain inimical concentration of hydrogen ions, as Mines (1913) supposed, was left an open question by Ashman, and still remains so.

Mobitz (1924, 1928) defined the Wenckebach type of A-V block as Type I, usually functional in pathogenesis, and adduced evidence to show that Type II, known now as the Mobitz type, in which dropped beats occur without previous prolongation of the P–R interval, is usually due to organic interruption of the A-V junction. However, he admitted the not infrequent association of the two types in the same record. Experimentally it has also been

pointed out that transitions from Type I to II may be obtained by increasing the rate of stimulation in digitalized ventricular strips (Schellong, 1924) and likewise in the A-V node and bundle (Scherf and Shookhoff, 1925). Even Wenckebach (1903, 1906), however, leaned toward a different explanation for Type II block, viz., diminished excitability. This explanation has been championed by Hay (1906) for both types of A-V block, and recently accepted as one factor by Campbell (1943).

Heim (1936) published recovery curves based upon Shellong's work (1924) with digitalized frog ventricle muscle strips, and compared them with curves, drawn separately for each Wenckebach period, from patients with Wenckeback type of A-V block due to digitalis administration. In both he frequently found a relatively vertical part of the recovery curve in the middle of the Wenckebach period, in which the P–R interval was prolonged without any marked shortening of the R–P interval. He interpreted this to mean sudden prolongation of the absolute and relative refractory periods from beat to beat. Blumberger (1937) has also drawn similar recovery curves of conductivity in two cases of Wenckebach block, which purported to show some changes in refractoriness from beat to beat.

We have published (1943) recovery curves in a case of reciprocal rhythm, showing the effects of various chemical and nervous influences on the A-V node. In general they resembled the recovery curves of Mobitz (1924), Lewis and Master (1925), Ashman (1925), and Schellong (1924, 1931) in their logarithmic form and absence of momentary variations of any great degree. We have seen such momentary variations in refractoriness in one case (1944), but do not believe that they are the basic mechanism that leads to Wenckebach periods.

Results. (A) Recovery Curves from Clinical Cases

Diagrams that represent recovery of A-V conductivity may readily be constructed by plotting the P–R interval against the preceding R–P interval. These values are obviously not exact measurements of either the conduction time through the A-V node, or the recovery time of these tissues, since they include the time intervals required for the passage of each impulse from the S-A node to the A-V node, and also that required for transmission from the A-V node to the ventricular muscle. Hence the curves obtained are at best approximations, but since the errors involved are probably reasonably constant, the approximations may be regarded as satisfactory and usable.

In general, recovery curves obtained in this fashion are logarithmic in contour. There are many factors that vary from case to case. Our files contain about 50 cases showing partial heart block of the Wenckebach type. In most instances, the patients had had rheumatic or arteriosclerotic heart disease, occasionally with recent myocardial infarction, or had been given digitalis, often in excessive amounts. Digitalis over-dosage was also a factor in the precipitation of paroxysmal auricular tachycardia in a large series of cases previously reported (1943), many of whom showed the Wenckebach type of block, a fact that suggested to us the importance of the auricular rate in the pathogenesis of heart block. In 30 cases, and often in multiple curves, the P waves were sufficiently clear-cut to allow the measurements necessary for the construction of recovery curves. In Fig. 1 we have assembled several of these curves for the purpose of illustrating two points: (1) the individual curves are smooth, without the humps described by Heim (1936) and Blumberger (1937); and (2) the curves show, as a group, tremendous variation in contour and position in the co-ordinate system. Fig. 2 shows curves drawn for consecutive Wenckebach periods in three patients. They illustrate further our failure to observe the type of curve shown by Blumberger and Heim. They also serve to show that whereas the general type of the curve is smooth and constant from moment to moment, the individual points show sufficient variation to indicate that minor influences may affect the exact extent of recovery during each cardiac cycle. These play roles difficult to evaluate, but we consider them in general unimportant in comparison with the physiological attributes of the conduction tissue that are expressed by the recovery curve.

Ventricular premature beats, as is well known, may affect subsequent A-V conduction. Thus in the middle curve of Fig. 2, a point obtained from a cycle following a ventricular premature beat shows much delayed conduction. Conversely, improved conductivity is seen in the location of points above and to the left of the curve when Wenckebach block

P R Interval

P R Interval

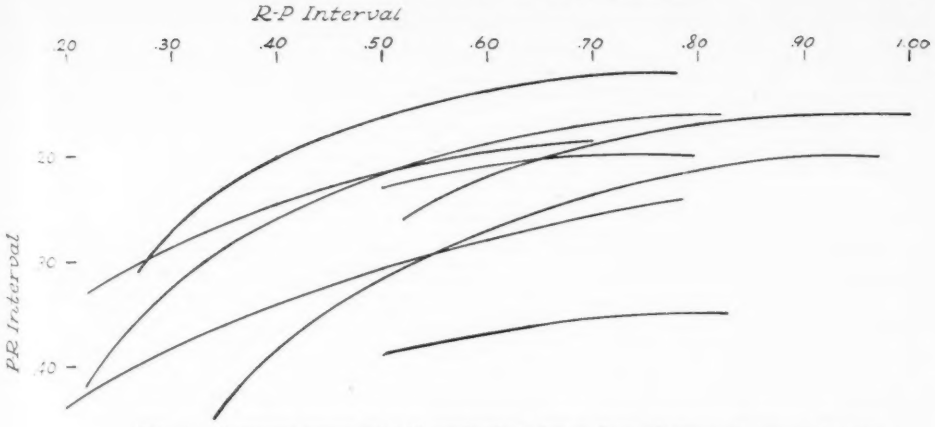

FIG. 1.—Recovery curves of A-V conduction, drawn from electrocardiograms showing the Wenckebach type of block, by relating the P–R intervals to the preceding R–P interval.

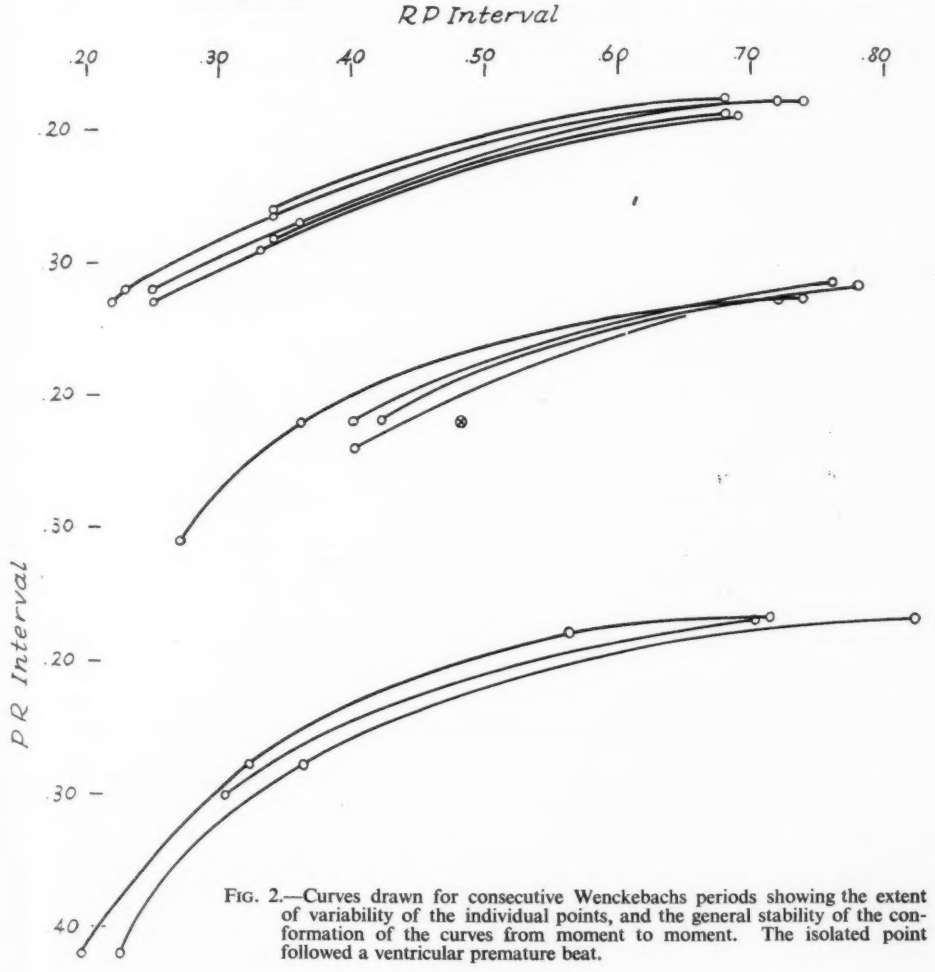

FIG. 2.—Curves drawn for consecutive Wenckebachs periods showing the extent of variability of the individual points, and the general stability of the conformation of the curves from moment to moment. The isolated point followed a ventricular premature beat.

suddenly changes to 1 : 1 conduction, possibly through reflex diminution in vagal tone. It seems probable that the exact location of each point may be slightly affected by reflex vagal and sympathetic influences, the respiratory cycle, the carotid sinus reflex, and cyclic local metabolic changes. Although these and similar factors may—and undoubtedly do—produce minor changes in refractoriness, recovery, and conductivity, we do not believe that they are fundamental to the mechanism that leads to the Wenckebach type of block.

(B) Theoretical Recovery Curves

Inspection of recovery curves derived from clinical cases exhibiting the Wenckebach phenomenon reveals a wide variation in several particulars: the absolute refractory period, the contour of the curve during recovery, the time required for complete recovery, and the conduction time after complete recovery. It is obvious that an additional variable factor, i.e. the auricular rate, must also govern the time available for recovery of the conducting tissues, and hence affect the degree of A-V block. These considerations have led us to select four arbitrarily drawn recovery curves, all with the same absolute refractory period of 0·20 sec., and the same conduction time of 0·20 sec. after complete recovery, but with slopes varying from rapid to slow recovery. Using each curve, the effect of varying auricular rate upon the P–R interval has been studied.

As a starting point for each set of calculations, the assumption has been made that a blocked impulse has fallen just within the absolute refractory period, 0·19 sec. after the preceding R wave. This allows the further assumption of a maximal rest period before the set of complexes with which calculations are begun. In other words, an initial R–P interval is assumed of 0·19 sec. plus the P–P interval being studied. With these premises, the theoretical recovery curves in Fig. 3 have been used to calculate the A-V conduction times for many different auricular rates by reading from the curve the P–R interval that corresponds to each R–P interval. Several examples will make this procedure clear.

1. Curve A; auricular rate 80 a minute (P–P interval 0·75 sec.); maximal possible recovery time 0·75 + 0·19, or 0·94 sec.

R–P interval	P–R interval	Next R–P interval
0·94	0·20	0·75 − 0·20 = 0·55
0·55	0·20	0·55
0·55	0·20	etc., . . .

Hence, at this auricular rate, the P–R interval will always be 0·20 sec.

2. Curve A; auricular rate 109 a minute (P–P interval 0·55 sec.); maximal possible recovery time 0·55 + 0·19, or 0·74 sec.

R–P interval	P–R interval	Next R–P interval
0·74	0·20	0·55 − 0·20 = 0·35
0·35	0·217	0·55 − 0·217 = 0·333
0·333	0·224	0·55 − 0·224 = 0·326
0·326	0·227	0·55 − 0·227 = 0·323
0·323	0·228	0·55 − 0·228 = 0·322
0·322	0·228	0·55 − 0·228 = 0·322
0·322	0·228	etc. . . .

Hence, at this auricular rate, the P–R interval will become stabilized at 0·228 sec.

3. Curve A; auricular rate 120 a minute (P–P interval 0·50 sec.); maximal possible recovery time 0·50 + 0·19, or 0·69 sec.

R–P interval	P–R interval	Next R–P interval
0·69	0·20	0·50 − 0·20 = 0·30
0·30	0·24	0·50 − 0·24 = 0·26
0·26	0·267	0·50 − 0·267 = 0·233
0·233	0·295	0·50 − 0·295 = 0·205
0·205	0·36	0·50 − 0·36 = 0·14
0·14	blocked	0·50 + 0·14 = 0·64
0·64	0·20	0·50 − 0·20 = 0·30
0·30	0·24	etc. . . .

Hence, at this auricular rate, there is a 6 : 5 A–V block of the Wenckebach type.

4. Curve D; auricular rate 102 a minute (P–P interval 0·59 sec.); maximal possible recovery time 0·59+0·19, or 0·78 sec.).

R–P interval	P–R interval	Next R–P interval
0·78	0·20	0·59−0·20 =0·39
0·39	0·312	0·59−0·312=0·278
0·278	0·362	0·59−0·362=0·228
0·228	0·385	0·59−0·385=0·205
0·205	0·397	0·59−0·397=0·193
0·193	blocked	0·59+0·193=0·783
0·783	0·20	etc. . . .

Using curve D, 6 : 5 block occurs at a slower auricular rate than for Curve A.

5. Curve D, auricular rate 120 a minute (P–P interval 0·50 sec.); maximal possible recovery time 0·50+0·19, or 0·69 sec.

R–P interval	P–R interval	Next R–P interval
0·69	0·20	0·50−0·20 =0·30
0·30	0·352	0·50−0·352=0·148
0·148	blocked	0·50+0·148=0·648
0·648	0·217	0·50−0·217=0·283
0·283	0·36	0·50−0·36 =0·14
0·14	blocked	0·50+0·14 =0·64
0·64	0·219	etc. . . .

Using Curve D, this auricular rate results in a 3 : 2 Wenckebach block.

Table I summarizes the data obtained in this fashion for each curve, and over a wide range of auricular rates.

Comparison of the theoretical curves in Fig. 3 with the curves from clinical sources in Fig. 1, indicates that much longer refractory periods and less complete recovery than has been assumed in constructing Fig. 3 are commonly encountered clinically. For example, if we assume, as seems well justified by Fig. 1, an absolute refractory period of 0·40 sec., and a P–R interval of 0·30 sec. at complete recovery, and employ a curve of the contour of curve D, we find that similar grades of block are obtained with much lower auricular rates.

6. Curve D, auricular rate 67·5 a minute (P–P interval 0·89 sec.); maximal possible recovery time 0·89+0·39, or 1·28 sec.

R–P interval	P–R interval	Next R–P interval
1·28	0·30	0·89−0·30 =0·59
0·59	0·412	0·89−0·412=0·478
0·478	0·462	0·89−0·462=0·428
0·428	0·485	0·89−0·485=0·405
0·405	0·497	0·89−0·497=0·393
0·393	blocked	0·89+0·393=1·283
1·283	0·30	etc. . . .

These physiological constants produce a 6 : 5 block at a slower auricular rate than in example 4.

7. Curve D, auricular rate 75 a minute (P–P interval 0·80 sec.); maximal possible recovery time 0·80+0·39, or 1·19 sec.

R–P interval	P–R interval	Next R–P interval
1·19	0·30	0·80−0·30 =0·50
0·50	0·452	0·80−0·452=0·348
0·348	blocked	0·80+0·348=1·148
1·148	0·30	etc. . . .

Hence, we derive a 3 : 2 block at this auricular rate, which is much slower than in example 5.

These examples suffice to show that the grades of block listed in Table I may readily be anticipated at auricular rates well within the range of those observed clinically.

Similar depression of the conducting tissues with prolonged refractoriness and delayed recovery will account for the presence of the higher grades of A-V block at auricular rates much lower than those required in Table I. An absolute refractory period of 0·60 sec., and a P–R interval at complete recovery of 0·40 sec., permits the calculation of a block as high as 6 : 1. We have encountered (1943) one example of 6 : 1 block in a patient with paroxysmal tachycardia whose conducting tissues were reflexly depressed by carotid sinus pressure.

To return to Table I, certain general observations should be made.

TABLE I

CALCULATED DEGREE OF A-V BLOCK FOR VARYING AURICULAR RATES

P–P interval	Curve A	Curve B	Curve C	Curve D
0·90				0·20
0·89				0·206
0·85				0·223
0·80			0·20	0·250
0·79			0·202	0·255
0·75			0·213	0·277
0·70		0·20	0·242	0·312
0·69		0·202	0·247	0·327
0·65		0·213	0·287	0·352
0·60	0·20	0·258	0·382	0·398
0·59	0·205	0·277	9 : 8	6 : 5
0·58	0·210	0·322	7 : 6	5 : 4
0·57	0·215	12 : 11	6 : 5	4 : 3
0·56	0·222	8 : 7	5 : 4	4 : 3
0·55	0·228	7 : 6	4 : 3	4 : 3
0·54	0·238	5 : 4	4 : 3	4 : 3
0·53	0·255	5 : 4	4 : 3	3 : 2
0·52	13 : 12	4 : 3	3 : 2	3 : 2
0·51	7 : 6	4 : 3	3 : 2	3 : 2
0·50	6 : 5	4 : 3	3 : 2	3 : 2
0·49	5 : 4	3 : 2	3 : 2	3 : 2
0·48	4 : 3	3 : 2	3 : 2	3 : 2
0·47	4 : 3	3 : 2	3 : 2	3 : 2
0·46	3 : 2	3 : 2	3 : 2	3 : 2×4 2 : 1×1
0·45	3 : 2	3 : 2	3 : 2	3 : 2×1 2 : 1×1 3 : 2×1
0·44	3 : 2	3 : 2	3 : 2	2 : 1×1
0·43	3 : 2	3 : 2	3 : 2×1 2 : 1×1	3 : 2×1 2 : 1×2
0·42	3 : 2	3 : 2	3 : 2×1 2 : 1×1	2 : 1
0·41	3 : 2	3 : 2×1 2 : 1×1	3 : 2×1 2 : 1×1	2 : 1
0·40	3 : 2	3 : 2×1 2 : 1×1	3 : 2×1 2 : 1×3	2 : 1
0·39	2 : 1	2 : 1	2 : 1	2 : 1
0·38	2 : 1	2 : 1	2 : 1	2 : 1
0·37	2 : 1	2 : 1	2 : 1	2 : 1
0·36	2 : 1	2 : 1	2 : 1	2 : 1
0·35	2 : 1	2 : 1	2 : 1	2 : 1
0·34	2 : 1	2 : 1	2 : 1	2 : 1
0·33	2 : 1	2 : 1	2 : 1	2 : 1
0·32	2 : 1	2 : 1	2 : 1	2 : 1
0·31	2 : 1	2 : 1	2 : 1	2 : 1
0·30	2 : 1	2 : 1	2 : 1	2 : 1
0·29	2 : 1	2 : 1	2 : 1×4 3 : 1×1	2 : 1×2 3 : 1×1
0·28	2 : 1	2 : 1×5 3 : 1×1	2 : 1×3 3 : 1×1	2 : 1×1 3 : 1×1
0·27̇	2 : 1	2 : 1×3 3 : 1×1	2 : 1×2 3 : 1×1	2 : 1×1 3 : 1×1
0·26	2 : 1	2 : 1×2 3 : 1×1	2 : 1×2 3 : 1×1	2 : 1×1 3 : 1×1
0·25	2 : 1	2 : 1×1 3 : 1×1	2 : 1×1 3 : 1×1	2 : 1×1 3 : 1×3
0·24	2 : 1×2 3 : 1×1	2 : 1×1 3 : 1×1	2 : 1×1 3 : 1×2	3 : 1
0·23	2 : 1×1 3 : 1×1	2 : 1×1 3 : 1×2	2 : 1×1 3 : 1×3	3 : 1
0·22	2 : 1×1 3 : 1×1	2 : 1×1 3 : 1×3	3 : 1	3 : 1
0·21	2 : 1×1 3 : 1×3	3 : 1	3 : 1	3 : 1
0·20	3 : 1	3 : 1	3 : 1	3 : 1

TABLE I.—Calculated P–R intervals and grades of A-V block, obtained at the auricular rates indicated, calculated from the curves of Fig. 3 in the manner described in the text. Admixtures of block are indicated; for example, 3 : 2 alternating with 2 : 1 block is listed as 3 : 2×1/2 : 1×1.

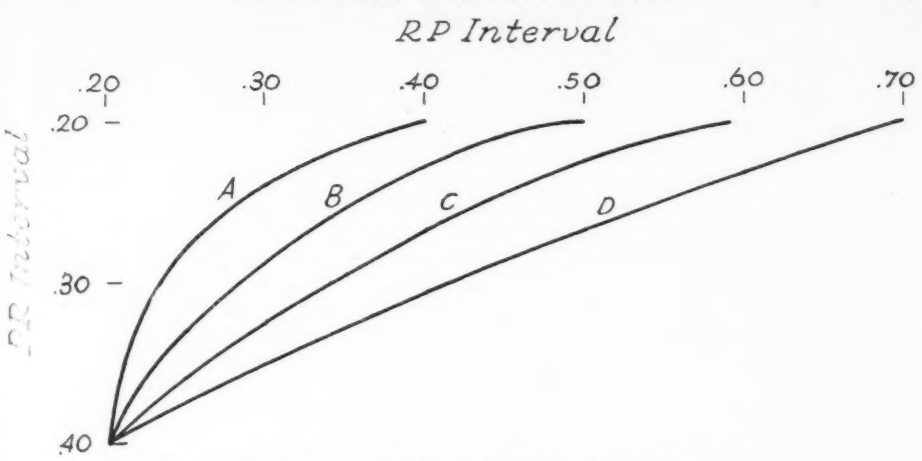

FIG. 3.—Idealized curves, used for the calculations described in the text.

1. Variations in the auricular rate, for each of the recovery curves studied, lead to a wide variety of conduction disturbances. With increasing auricular rates, A-V conduction is progressively impaired.

2. At slow rates, whenever the P–P interval is such that the resulting R–P interval falls in the range of complete recovery, the P–R interval is normal.

3. At slightly faster rates, whenever the resultant R–P interval falls in the range of partial refractoriness, or incomplete recovery, there is partial heart block with prolongation of the P–R interval. This is longer with the curves of less rapid recovery, i.e. longest with curve D. The limiting factor is the P–R interval at R–P intervals just exceeding the refractory period, and with our curves could not exceed 0·40 sec. Under other conditions, the longest P–R interval without dropped beats could be longer than 0·40 sec., and, of course, not infrequently is much greater. As the curves show progressively slower recovery, prolongation of the P–R interval without dropped beats is possible only at slower and slower rates, since dropped beats occur more readily.

4. Further shortening of the P–P interval leads to low grade A-V block, with dropped beats of the Wenckebach type. At any given auricular rate in this range, the degree of block is higher as we pass from curve A to curve D.

5. As the P–P interval is further shortened, 2 : 1 block is found, first mixed in varying proportions with 3 : 2 block, and then for a wide span of auricular rates as simple 2 : 1 block. At still higher auricular rates 3 : 1 block appears, first in admixture with 2 : 1 block, and finally, alone.

6. At any auricular rate, the grade of block is highest with curve D, which shows slowest recovery. Even higher grades of block, at the same auricular rate, may be found if the curve D is shifted down and to the right in the direction of further depression of conductivity and recovery. This is shown in examples 6 and 7, above.

7. In general, the flatter the contour of the recovery curve, as in curves C and D, the more typical of the classical Wenckebach period are the consecutive P–R intervals. This is illustrated in example 4 above, derived from curve D, which is to be contrasted with example 3, derived from curve A. In the latter, the greatest prolongation of the P–R interval is seen at the end of the Wenckebach cycle, just before the dropped beat; in the former, the P–R intervals show typically the greatest increase in the second complex of the group. This is consistently borne out in all of the calculations upon which Table I is based. This is due to the fact that near the absolute refractory period, curve A has a more vertical slope than curve D.

COMMENT

Cardiac physiologists have variously attempted to explain the Wenckebach type of partial heart block on the basis of changing properties of the conducting tissues. They have postulated momentary changes in excitability, latency, the absolute or relative refractory periods, recovery of excitability or of conductivity, and increasing rate of stimulation, produced by experimental factors, drugs, or myocardial disease. The latency theory is no longer considered tenable; possible changes in excitability are not accessible to clinical study; nor do we believe that momentary changes in refractoriness or conductivity need be invoked to explain the mechanism of Wenckebach block. The role of certain of the physiological properties of the heart muscle has been appreciated, but a unified concept has hitherto been lacking. Schellong was clearly aware of the importance of the relative refractory period as reflected in the recovery curve of excitability, and of the frequency of stimulation. Mobitz and Ashman demonstrated the effect upon the P–R interval of the preceding recovery time. Numerous authors have emphasized the importance of increasing auricular rates.

Studies of clinical material permit the evaluation of the following factors that determine the sequence of A-V conduction in the Wenckebach type of block:

1. Duration of complete refractoriness.
2. Duration of partial refractoriness.
3. Contour of the recovery curve.
4. Conduction time after complete recovery.
5. Auricular rate (P–P interval).

It should be emphasized that the first four factors listed actually are encompassed by the curves of recovery of A-V conductivity. For this reason we consider these curves fundamental to any attempt at explanation of Wenckebach block. We have demonstrated above that all varieties of Wenckebach block may be deduced by varying these five factors, i.e. the recovery curve and the auricular rate. In fact, other varieties of partial A-V block seem to be susceptible to explanation on the same basis (Table I).

The curves of Fig. 3 are not purely artificial; they are idealizations of the several varieties of curves that were drawn from clinical cases, and represent some of the possible fluctuations in speed and completeness of recovery. Their contour and co-ordinate values are typical of many of the recovery curves published previously, both by ourselves and other authors. By assuming certain auricular rates, curves may be drawn from Campbell's formula (1943) for the length of consecutive P–R intervals; these resemble our curve C or, to a lesser extent, curve B. The admixture in all proportions of closely adjoining grades of block, such as 3 : 2 with 2 : 1, or 2 : 1 with 3 : 1, seen in Table I, is also encountered clinically. The frequency with which the various grades of block are found in Table I, as well as their stability over a wide range of auricular rates, agree well with clinical experience.

Cases are encountered clinically that show marked transitions in the grade of block, sometimes cyclic in character, e.g. from 4 : 3 to 2 : 1, or from 3 : 2 to 1 : 1, and back again. These shifts cannot be deduced from a single recovery curve, and require the assumption of transient change in those myocardial properties that fix the recovery curve. These changes in refractoriness and recovery and, equally important, in the auricular rate—may be due to a wide variety of chemical or reflex nervous factors. Similar factors, as we have pointed out above, may well be responsible for the minor deviations of individual points from the smooth recovery curves of clinical cases. The point at which these otherwise minor deviations are most conspicuous is at the absolute refractory period, where there may be some overlapping of the R–P intervals of conducted and dropped beats.

The five factors that we have listed above, which determine the character of the Wenckebach periods, are mutually interdependent and may change simultaneously in the same or opposite directions. Thus, acceleration of the auricular rate, which would tend to increase A-V block, in itself shortens refractoriness and recovery (Lewis and Master, 1925), in effect shifting the recovery curve upwards and to the left. Increased vagal tone shifts the recovery curve in the direction of less rapid recovery and greater block, but may be associated with a slower auricular rate, which would allow more complete recovery. These momentary shifts in refractoriness from beat to beat, correlated with changing recovery times, have

served Lewis and Master, and Rothberger as the entire basis for their explanations of Wenckebach block. Our data show it is unnecessary to invoke such shifts to explain the Wenckebach phenomenon.

Aside from these minor variations, the recovery curve of the typical case of Wenckebach block is smooth in contour, and shows remarkable stability in the absolute and relative refractory periods, and in the A-V conduction time after complete recovery. Under these circumstances, variations in the auricular rate assume paramount importance in determining the grade of block in the Wenckebach periods at any time. Contrary to the reports of Heim and Blumberger, in our experience neither the contour of the recovery curves, nor their place in the co-ordinate system, change significantly from cycle to cycle in the typical case.

On the other hand, the diverse recovery curves of different patients, or of the same patients under different circumstances, account for the varying degrees of block that may occur at the same auricular rate. Thus, with one recovery curve, the P–R interval may reach a maximum of 0·30 sec. before a dropped beat, while with another curve, there may be 1 : 1 conduction with a constant P–R interval of 0·45 sec., or higher. This same type of phenomenon may occur, with a constant recovery curve, as a result of variation in the auricular rate.

It has been noted by other observers, both clinically and experimentally, that the Type II block of Mobitz is occasionally seen in association with the Wenckebach Type I block. Since all varieties of partial A-V block, with the exception of Type II, are seen in Table I to have the same fundamental explanation in terms of the auricular rate and the recovery curve of A-V conduction, it seems probable that Type II would have the same physiological basis. We have had no instance available for study, but we suggest the possibility that this type of block occurs when the recovery curve is an almost horizontal straight line, from the absolute refractory period to the end of recovery. We would predict, if this assumption were true, that minute increments of the P–R interval precede the sudden dropped beat. If this is not true, the explanation must depend on sudden changes in refractoriness of the severely damaged conducting tissues. Sudden changes in excitability seem to us to have no clinical or experimental support or parallel.

The empirical formula developed for Campbell by Professor Rushton for the prediction of consecutive P–R intervals in the average Wenckebach period, serves to emphasize that the block progresses according to a simple logarithmic law. As mentioned previously, logarithmic recovery curves may be drawn from this formula by assuming an auricular rate. This formula fixes the P–R interval at complete recovery, the longest P–R interval before dropped beats occur, and the duration of recovery. For each grade of block, the conformation of the recovery curve is likewise fixed, and as the grade of block decreases, with more rapid ventricular rates, the curves show a shift to the left. However, the formula does not fix the position of the curves in the co-ordinate system, and with this the absolute and relative refractory periods. These vary with the auricular rate assumed. We have been impressed with the wide diversity of the form and position of our clinical recovery curves, as well as the crucial significance of variations in the auricular rate. In the face of so many variables, we have not attempted to formulate a comprehensive mathematical expression for them all.

Summary

The Wenckebach type of partial A-V block is explained on the basis of varying auricular rates and varying curves of recovery of A-V conductivity. Other varieties of partial A-V block seem to be explicable in the same fashion.

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This is another Dr. K. did not see this work

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HYPOXÆMIA TESTS IN CORONARY DISEASE

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Many people have suffered from anginal pain and have still lived to old age. Cardiac infarction may set in suddenly after having been for a long time foreboded by a typical angina pectoris: on the other hand, a person may without any warning whatever fall prey to a lethal infarct. The dramatic character of the picture of the coronary heart disease and its capricious appearance raise the following two questions. How can one make an early diagnosis on the basis of the changes that form the substratum of the disease in order to permit a timely recourse to prophylactic measures? Can refined diagnostic measures dispel the anguish many people feel owing to the dread of this disease? Apart from electrocardiograms common clinical examination is not of much use. The history is the chief factor, but people differ in sensitivity to pain, in the faculty of observation, and in exactness of description. No wonder that attempts have for a long time been made to create a practical and objective method of testing the coronary function. Two principles have been applied in the first place, viz. electrocardiograms after respiration of air lacking in oxygen (by a gas mixture with diminished oxygen pressure or general under pressure), and after exertion.

Since the former method, referred to as the "hypoxæmia* test" by us, has now been employed for more than three years, it has seemed desirable to submit a few preliminary figures collected during the years 1942–44, to supplement the experiences so far available of the test as a practical method in clinical work. For reasons of space, I must limit myself to a statement of the figures without further critical remarks except the most necessary ones.

In 1933, Dietrich and Schwiegk found pathological features in the cardiogram after breathing air deficient in oxygen. Kai Larsen (1938) at Warburg's clinic in Copenhagen, performed 192 hypoxæmia tests on 133 subjects, 28 of whom were healthy and 43 suspected of coronary heart disease. The oxygen percentage in the inspiration air was 9 per cent, the test lasting for 6–8 minutes. As regards cases with coronary symptoms, he found 4 positive tests in 10 instances with a normal cardiogram at rest and 5 positive tests in 10 others with but small changes in the cardiogram at rest; in another 4 cases in the latter group, a positive cardiogram with exertion was noted. In the U.S.A., Levy, Barach, and Bruenn (1938) gave an account of their first investigations regarding the effect of hypoxæmia on the circulation. The work was supplemented in 1940 by Levy, Bruenn, and Williams with studies of the effect of drugs during hypoxæmia tests. Those studies were pursued in 1941 by reports from Levy, Bruenn, Williams, and Carr on 326 tests with 10 per cent oxygen for 20 minutes in 262 cases, 115 of whom were healthy and 147 suffered from cardiac disease, 79 of the latter having suspected or certain coronary heart disease. They obtained from 18 to 69 per cent positive tests, relative to the degree of the coronary symptoms and the appearance of the cardiogram at rest.

In Sweden, Nylin (1943) has earlier presented some data from 163 private patients with 22 per cent positive tests. Åkesson and Malmström (1945) have recently published some cases of cardiograms after exertion when breathing air deficient in oxygen. The hypoxæmia test in one form or another has also been adopted for clinical purposes elsewhere in this country.

* The term hypoxæmia has been used throughout instead of anoxæmia, which is most common in the Anglo-Saxon literature, because the former has been considered more adequate in this connection.

Methods and Grouping of Patients

The material which will be discussed in the present paper comprises 350 hypoxæmia tests carried out on a total of 326 patients examined during the years 1942–44 at the Sabbatsbergs Sjukhus: 166 of these patients were men and 160 women; 43 of the total number of patients were under 30 years of age, 40 between 31–40, 88 between 41–50, 88 between 51–60, 54 between 61–70, and 13 above 70 years of age. In 1942, 87 cases were examined, 8 being positive, i.e. 9 per cent, and in 1943, 140 cases, 20 being positive, i.e. 14 per cent, and in 1944, 114 cases with 20 positive tests, i.e. 17 per cent. The indications for the use of the test have probably been gradually stabilized.

The technique employed here conforms to that adopted by Levy *et al.* (1938, 1940) viz. inspiration of a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes. Nylin has described the details earlier. The patient, who has not eaten for some hours, is placed on an examination couch and inhales the gas compound through a mouthpiece connected with a Lovén mask while a nose clip is adapted. The patient is informed of the nature of the test, of the discomforts that may appear, and requested to breathe calmly and give a signal with the hand to the assistant if the discomforts should become too severe. A cardiogram is taken at rest before the test and after 20 minutes or earlier if the test should have to be abbreviated. Immediately after the test, the patient is given 100 per cent oxygen-gas for as long as necessary.

The gas mixture was delivered during the first years in bombs containing 10 per cent O_2 and 90 per cent N_2. According to analyses which have been performed, the oxygen content has varied within the limits $10 \pm 0{\cdot}3$ per cent. During the second half of the year 1944, the gas-mixture bomb was replaced by a gas-mixing apparatus, constructed at Aga by Andersson, civil engineer, according to Nylin's directions, the principle of which will be seen in the diagram (Fig. 1). Pure nitrogen gas runs through an injector (3) into a gas current-meter (5)

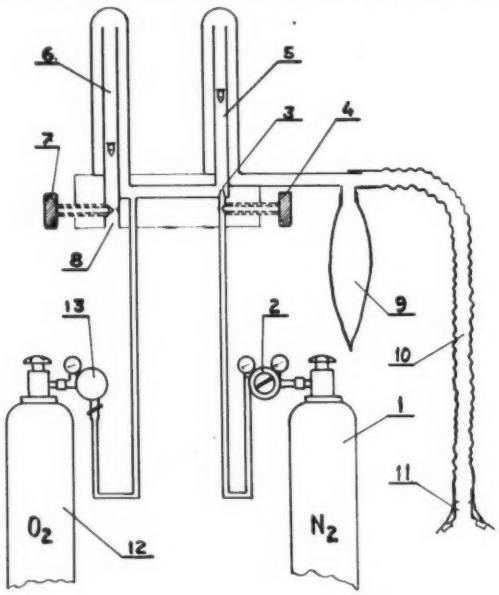

Fig. 1.—Diagram of gas-mixing apparatus (see text).

which draws in by means of suction a quantity of indoor air (8) which can be made equal to the nitrogen gas quantity by manipulation of the floats (4, 7) in the two gas current-meters. Since the hypoxæmia tests are performed in fresh indoor air with an oxygen content of 20 per cent, the oxygen-gas content in the gas mixture will, accordingly, be half of it, i.e.

Table I
Details of Hypoxæmia Tests (1942–44)

TABLE I
DETAILS OF HYPOXÆMIA TESTS (1942–44)

	Number of cases	Men	Women	Number of tests: Group A Normal rest curve			Group B Coronary rest curve			Group C Cardio-sclerotic rest curve		Group D Other changes in the rest curve			Number of cases: Doubtful tests		Positive tests		Exertion cardiogram			Negative HO but positive EC	Positive HO and positive EC	Positive HO but negative EC
				Negative	Doubtful	Positive	Negative	Doubtful	Positive	Negative	Doubtful	Positive	Negative	Doubtful	Positive	Number	Percentage	Number	Percentage	Negative	Doubtful	Positive			
Healthy somatically		16	11	5	16															10					
Other diseases without coronary disease		41	21	20	31	2	1	5	1		1		1			3	7·2	1	2·4	6					
Other diseases with suspected cor. dis.	79	33	16	17	18	1	3	4	4	2	1		2			5	15·1	5	15·1	6			1	1	1
Other diseases with probable cor. dis.		5	5		2		1*	1		2*	1							2	40	2		2			
Organic heart disease without cor. dis.		13	9	4	9				2				2			2	15·4			6					
Organic heart disease with suspected cor. dis.	31	16	7	9	6	1	1	2		1		1	3		1	1	6·3	4	25	3		2	1	1	
Organic heart disease with probable cor. dis.		2	2		1					1								1	50						
Hypertension without cor. dis.		28	12	16	12		1	10	3	1	1		1			3	10·7	2	7·1	2	2	1			
Hypertension with suspected cor. dis.	85	36	12	24	20	1	1	8	1	2	1		1		1	2	5·6	4	11·2	4	1	2	1		
Hypertension with probable cor. dis.		21	9	12	5	2	4*	3	3	4*	1				1*	5	23·8	7	33·3	3			2		
Other heart disease without cor. dis.		26	14	12	14	1	1	2			2		7			1	3·8	1	3·8	9		2			
Other heart disease with suspected cor. dis.	39	13	3	10	6		3*			1*		1	2	1	1	1	7·6	5	38·5	4		3	2	1	
Other heart disease with probable cor. dis.																									
Only symptoms resembling A.P.		25	15	10	21			1	1		1		2			1	4·0	1		4	1	1			
Suspected angina pectoris (A.P.)	66	33	14	19	21	1	5	3	3*	3*						4	12·1	8	24·2	11	1	1	1		
Certain angina pectoris (A.P.)		8	6	2	3	1	1	2	1	1						2	25·0	2	25·0	3		1	1		
Earlier infarction without A.P.	10	1	1					(1)					1												
	(18)	(2)		(1)																					
Earlier infarction with A.P. now		9	9		3			4	1	2						1	11·1	2	22·2	4		1	1		1
		(16)	(13)	(3)			(1)	(5)	(3)	(4)						(3)	18·8	(5)	31·3	(6)	(1)				
Infarction later in the course	(5)	(5)	(5)		(1)		(1)	(2)	(1)	(1)						(1)	20	(2)	40	(1)					
		326	166	160	188	10	22	45	20	20	9	2	22	1	4	31 cases (31 tests)		44 cases (48 tests)		77	5	16	11	5	2
																74 cases		(79 tests)		/=98/ Exposing HO tests = Gr. A+C+D.					
I. Healthy and without cor. dis. and the group "only symptoms resembling A.P."		149	82	67	103	3	3	18	7	1	5		14			10	6·7	4	2·7	Number of cases 127	Doubtful No. 3	Percentage 2·3	Positive No. 3	Percentage 2·2	
II. All cases with suspected coronary symptoms		131	52	79	71	4	13*	17	8*	9**	2	2	7	1	3	13	9·9	26	19·8	100	5	5·0	18	18·0	
III. All cases with probable or certain coronary symptoms		46	32	14	14	3	6**	10	5	10**	2		1		1*	8	17·4	14	30·4	26	3	11·5	6	23·1	
		326	166	160	188	10	22	45	20	20	9	2	22	1	4										

*=different results of the test in the same pat.
( )=present already in earlier clin. group.

Number of tests, 350. cor. dis.=coronary disease. A.P.=angina pectoris.

10 per cent. The oxygen-gas content obtained by this method will be at least equal in reliability to a ready mixture.

The cardiogram examined has, in practically all cases, also comprised one or several chest leads. In the course of these years, different chest lead procedures have been tried at the clinic. The predominant number of cardiograms have been performed with Nylin's anterior and posterior lead, some also with an inferior lead, as described earlier by Nylin and Grewin (1942). After the stabilization of the chest lead technique to only the anterior and posterior leads, all the five leads have been registered synchronously with the help of Elmqvist's five-lead electrocardiograph.

The indications for the hypoxæmia test have principally occurred in the following cases: suspected coronary cases, a mixed group of undifferentiated cases sent to our clinic for an estimation of the possible risks of operation, and cases from the State Insurance Board. The test has been regarded as contra-indicated in the event of infarcts within six months and in cases with failure. Nor has any patient been subjected to more than one test on one and the same day.

The earlier discussion dealt with, *inter alia*, the risks involved in the test. In this instance, experience has however been favourable. The majority of patients manifest, during the course of the test, a considerable general cyanosis. The deficiency in the oxygen saturation of the blood, as a rule, raises the frequency in the heart of, probably, about 25–40 per cent. Many patients, in fact, feel a moderately severe headache. Thus, these occurrences are to be expected and need not give rise to anxiety in the patient or the conductor of the test. Further, they are rapidly transient when the oxygen-gas has been turned on at the end of the test. As to the possibility of complications, two have occurred in our material, viz. firstly, mild anxiety in very nervous patients, and secondly, attacks of paleness, peripheral chill, bradycardia, sensation of choking, and general appearance of shock. In all likelihood, this is due to a vagal excitation in persons particularly predisposed to it. No technical error has been noted. Recently, two alarming cases of this kind have been observed, but no effect on the cardiogram other than bradycardia was detected. Both cases recovered quickly by means of adequate therapy. In this material a similar picture seems to have occurred in one case, also with a negative result of the test, but, on the other hand, with suspected anginal pains. The cases with a decrease in the heart frequency after 20 minutes may, perhaps, be milder equivalents to the forementioned case. They comprise another 13 with negative tests and one with a positive test. Thirdly, there may, conceivably, involve a risk of eliciting an infarct in a heart where this constitutes a latent threat. We have not been in a position to ascertain any such case, nor have I seen any mention of it in reports on the subject. On the other hand, suspected or typical anginal pains have appeared in 7 cases with positive tests, 6 of which have been interrupted after less than 20 minutes, and in 5 negative cases, 3 of which were interrupted prematurely. Infarction has not ensued from the test in any single case. An infarct was mentioned in the patient's history in one of the positive cases and in one of the negative ones which was interrupted prematurely. According to a newspaper notice, one patient died 13 days after an attempt to perform a hypoxæmia test which had had to be interrupted owing to pain without the registration of any curves. He had suffered from an anterior infarct two years earlier and had been incapable of work for a year on account of pain.

Apart from the first acute stage of a cardiac infarct, the coronary heart disease is more frequently, at the time of the examination, a latent condition than a manifest one. Thus the *raison d'etre* of a hypoxæmia test should be to confirm or remove, objectively and manifestly, any suspicion of the coronary heart disease that there has been reason to entertain on the basis of the patient's history.

Taking this into consideration, the present material has been classified in accordance with the patient's history and such simple clinical data as can be established by any physician, and not according to the clinical diagnosis arrived at after examination of the cardiogram and hypoxæmia tests of the patients concerned. Moreover, when the aim has been to " expose " a latent injury, in a cardiographic respect, a differentiation between the various tests has seemed most adequate in accordance with the appearance of the ordinary curve at rest. As regards the usefulness of the test compared with the ordinary cardiogram, a patho-

logical test after a normal ordinary record is of more importance than an accentuation of the curve of coronary insufficiency. The tests have therefore been divided into 4 groups, as follows: one with a normal cardiogram at rest, one with a coronary curve at rest,* another with a " cardiosclerotic " curve at rest (bundle branch block, low voltage), and, finally, one with some other change in the cardiogram at rest (principally arrhythmias). The test has been denoted as negative, doubtful, or positive, according to the outcome of the test. For practical reasons the following criteria of Levy *et al.* (1941) have been used with, however, a substitution of lead IVF for one of our chest leads.

Criteria for Positive Tests, according to Levy et al. (1941)

The test is positive when

(1) the lowering of the S–T segments in leads I, II, III, and IV F constitutes or exceeds 3 mm., or
(2) T I is inverted, altogether or partly, and the S–T segment in lead I is lowered at least 1 mm., or
(3) T IV is altogether inverted, irrespective of the S–T segment, or
(4) T IV is partly inverted and the S–T segment is lowered at least 1 mm.

Clearly affected tests, not fitting into Levy's scheme, have been referred to a "doubtful " group. Still, the exact tracing of the limits between these groups remains an open question which future follow-up examinations may solve. No definite patho-physiological quantitative correlation to the positive test is as yet known. On the contrary, Vesa's observations as well as our own have shown that considerable spontaneous variations occur on and off with regard to S–T segments and T waves. There is, reasonably, no cause to believe that a certain limit at all exists. The transitions are, probably, vague and therefore a separate group of doubtful tests may, for the time being, be justified, not least in consideration of later follow-up examinations.

The cardiograms have chiefly been studied only with regard to the S–T segments and the T waves. The distance from the extreme points of these parts of the curve to a horizontal line through the lowest level of the P–Q line has been measured within 0·5 mm.† Hypoxæmia tests cannot be estimated without millimetre measurement.

In order to be able to perform off-hand an arrangement of each case in the most correct clinical group with the guidance of the history of the patient and simple clinical data (with the exception of the cardiogram), extracts from the records in this respect have been made on one side of a so-called needle-card, while the cardiographic facts have been annotated on the back. Then, the whole material has been classified simultaneously in order to obtain the greatest possible uniformity. The clinical group has been marked on each card before turning it to analyse the cardiographic changes.

The clinical grouping has been intended to comprise the following cases:

(1) Somatically healthy persons.
(2) Cases of another disease (often consultation cases).
(3) Cases of organic heart disease (valvular diseases and endocarditis or myocarditis.)
(4) Cases of hypertension.
(5) Cases of other heart diseases (principally arrhythmias, thyrotoxicosis, etc.).
(6) Cases with symptoms of angina pectoris, without any other disease.
(7) Cases with earlier cardiac infarct.
(8) Cases with later cardiac infarct (5 cases included in other groups).

The groups 2–5 have been divided into sub-groups with regard to the presence or absence, respectively, of " coronary " symptoms (mainly anginal pains), the latter being denoted as " suspected " or " probable " according to the degree of severity of the symptoms. Group 6 has, almost analogously, been divided into a group with symptoms resembling angina

* This group has also comprised curves with a digitalis effect *or* coronary insufficiency or both.

† It would, of course, be ideal to refer to a horizontal line through the T–P line which constitutes the real iso-electrical line. However, for technical reasons, Larsen as well as Levy, and others, have had to use the P–Q distance as a starting-point for the measurements. This has also been necessary in the present material of curves.

pectoris, but with a very faint suspicion of it, one with more suspicious symptoms, and another group with certain symptoms of what is called angina pectoris. The infarcts in group 7 have been classified according to the appearance of angina pectoris in the after-course.

The distribution of the material may be seen from the table.

Results

The number of positive tests within each individual disease group seems to increase greatly according to the degree of clinical suspicion of the coronary heart disease.

When the whole material is distributed in the same way as the above-mentioned disease groups, the group where no (noteworthy) suspicion of a coronary heart disease occurs will have positive tests in 3 per cent of the cases, the group with suspected coronary heart disease will have positive tests in 20 per cent, and the group with probable or certain coronary heart disease in 30 per cent. When the cases which revealed coronary cardiographic changes already at rest are excluded from the calculation, the "exposing" hypoxæmia tests are obtained where the corresponding percentages equal 2, 18, and 23.

The cases with a pathological effect (positive tests) within the group with coronary curve at rest * will analogously amount to 4, 27, and 40 per cent.

The four cases in which the test turned out to be positive without any suspicion of a coronary heart disease comprised a man of 56 years with pulmonary emphysema and chronic bronchitis, a woman of 36 years with recently alleviated acute myocarditis and 2 women of 53 and 57 years respectively, with hypertension but no symptoms of angina.

Only 5 of the 18 cases with earlier infarction gave positive tests, all of which were still suffering from angina, while 13 cases gave negative or doubtful tests (the latter in 3 instances), 11 with and 2 without angina pectoris.

Seventeen of the 166 men disclosed positive tests, the corresponding figures for the women being 27 out of 160. The percentage distribution of male and female positive tests within the three main groups is, in group I, 1 and 5 respectively, in group II, 14 and 23 respectively, and in group III, 28 and 36 respectively.

When the total material is distributed according to age, the group under 30 years offers 16 per cent of cases with positive tests, the remaining groups being as follows: between 31–40 years 15 per cent, between 41–50 years 7 per cent, between 51–60 years 18 per cent, between 61–70 years 11 per cent, and above 70 years 23 per cent. It is remarkable that 7 cases out of 43 have had positive tests under the age of 30. They comprise a man of 29 years with hypercholesterinæmia and infarction later in the course of the disease, a woman of 16, and one of 21 years shortly after an acute myocarditis, 2 women of 22 and 27 years, respectively, with paroxysmal tachycardia, a woman of 22 without definite diagnosis (high sedimentation rate (Westergren)), and a woman of 24 with exogenous psychosis and sensations of fear.

When the material is distributed according to professions, a distinction being made between heavy and less heavy work, and a more indefinite group of housework, the percentage figure of positive tests will be 10, 13, and 17 per cent respectively.

When an enlargement of the heart is considered to occur, i.e. when the radiological volume of the heart exceeds 500 c.c./m.^{2} of body surface, among 18 cases with an enlarged heart in group I none had a positive hypoxæmia test, while 4 among 13 cases were positive in group II, i.e. 31 per cent. This also applies to 4 out of 8 cases in group III, i.e. 50 per cent. The corresponding figures, with regard to the cases with hearts of normal size in the several groups, were 3, 20, and 23 per cent respectively.

As regards cases with pulmonary disease and probably diminished pulmonary function, 1 out of 8 in group I and 1 out of 6 in group II had positive hypoxæmia tests.

* It is, of course, sometimes difficult to distinguish between coronary curves and those affected by digitalis. Eleven of the cardiograms denoted as coronary have been performed at a time when the patient had been given digitalis. It is doubtful in 4 cases whether earlier digitalis medication has as yet left any signs in the cardiograms. Thus, a possibility of digitalis influence has occurred only in 1 of the positive tests, 3 of the doubtful ones, and in 7 of the negative ones. Therefore, broadly speaking after considering the cases involved, a digitalis influence may be said not to be of any statistical significance in this material. When occurring, it must involve a slight increase in the percentage of positive tests at coronary cardiograms as compared with the figures stated above.

As already mentioned, 15 cases showed a decrease in the heart frequency after the test. Another 14, one of which later became positive, obtained a cardiographic improvement of the curve as compared with the cardiogram at rest.

So far 12 patients have been reported to have died. Two of them gave positive tests. One was found at autopsy to have a considerable coronary sclerosis as well as recent thrombosis. The other was not subjected to autopsy but had died within an hour in an anginal attack. One case with a doubtful test revealed at autopsy much dilatation of the right half of the heart but no coronary sclerosis. Two out of 8 cases with negative tests had coronary cardiograms at rest, unaffected by the test. One of them was examined post-mortem and showed extremely narrowed coronary vessels, the other died of an infarct 4 months after the test. Two cases had "cardiosclerotic" curve at rest. One of them showed, at autopsy, hypertrophy and dilatation of the heart, as well as moderate coronary sclerosis. The other died suddenly on the operation table after finished surgical intervention. No autopsy was performed. One patient with a normal cardiogram at rest had very slight coronary sclerosis and was considered to have died of an Adams-Stokes attack. Two have died of decompensated mitral valve disease. One was examined post-mortem and revealed a typical mitral heart but no narrowing of the coronary vessels. One patient died of pulmonary carcinoma and was not subjected to autopsy. Finally, one patient died at home 13 days after the test; he had earlier had an infarct and suffered such severe pains at the test as to necessitate its interruption without any registration of the curve: as far as is known, no autopsy was performed.

A positive test has later become negative in 4 instances. This has happened in the following cases: a man of 52 years with Bürger's disease, and another man of 67 years with certain angina pectoris, possibly with earlier infarction, who died later of a second infarct, as well as 2 women of 22 years of age, one with paroxysmal tachycardia and the other with no definite diagnosis. In the latter case the test improved parallel to the sedimentation rate and the clinical picture.

Exertion tests have been carried out in not quite a third of the number of cases, usually at the same pace as has been endured by the patient at the function test according to Nylin. These tests have often seemed difficult to judge on account of the tachycardia. When the tests, in which one S–T segment has been lowered to 1 mm. or more, or a T wave has been inverted (probably a very liberal interpretation) are regarded as positive tests, 16 out of 98 have turned out positive. The exertion cardiogram has been positive in 11 cases, while the hypoxæmia test has been negative, the condition being reversed in two instances. These figures do not, as yet, permit the drawing of any conclusions. However, it is possible that the hypoxæmia test and the exertion test affect the myocardium in different ways.

Discussion

Larsen's investigations have been performed on the basis of a different method. Levy *et al.* have, in their clinical classification, also taken into account the appearance of the cardiogram at rest. My figures cannot, therefore, be directly comparable to those obtained by them. However, the figure 20 per cent of positive tests for the whole of group II should correspond approximately to Levy's 18 per cent. Further, the figure 40 per cent in my material should answer to Levy's 55 per cent of positive tests at coronary sclerosis with angina and an abnormal cardiogram.

Finally, the question arises whether the results will repay the extra work and risks entailed in the method. The answer, of course, partly depends on the importance attached to the prognostic value of the positive hypoxæmia test. Is the artificial electrocardiographic coronary insufficiency, which may be in some cases brought about, a manifestation of a deteriorated coronary circulation and reserve even under physiological conditions? Levy describes a positive case where the autopsy revealed coronary sclerosis, and another case where death ensued owing to an infarct. The same applies in our material to the two positive cases where death has been reported. So far the material has been too restricted for critical conclusions but does, nevertheless, offer some indications. Also the question remains open whether it is less dangerous for a patient with angina pectoris to have a negative test than a

positive one. For the time being, care is advised in drawing conclusions from negative tests. In my opinion, the test has much to offer, for the diagnostic methods hitherto employed in this disease are inadequate and in urgent need of effective additions.

Finally, attention should be directed to future potentialities. The hypoxæmia test appears to " expose " several coronary cases which escaped notice at the simple cardiogram at rest. The same may apply, nevertheless, also to one or two cases which are not coronary in the actual sense. Still other coronary cases may escape notice at the hypoxæmia test. What is the reason for the varying outcome of the test? What factors play a part in this respect at the exchange of gas in the lungs, the heart and, perhaps, also in the central nervous system? The question may be asked, whether a local or general occurrence of the anatomical or functional insufficiency determines the electrical manifestation of the myocardial reaction towards the hypoxæmia stimulation. Such problems and many others in addition remain to be solved. The answer must be the outcome of various contributions from animal experiments, studies of autopsy material, and modifications and improvements of the technique. The latter refers, *inter alia*, to the discovery of the most suitable oxygen pressure in the gas mixture and control of the arterial oxygen saturation and the pH of the blood during the tests (which is certainly not the same in different patients according, i.e., to their technique of breathing).

Summary and Conclusions

After a brief retrospect of earlier examinations, a report is given of the particular technique used in hypoxæmia tests at the Sabbatsberg Sjukhus. The results obtained from 350 tests on 326 patients during the period 1942–44 are demonstrated. The number of positive tests is found to increase pronouncedly in accordance with the degree of clinical suspicion of a coronary heart disease. Thus, positive tests occur in only 3 per cent in the group without a suspected coronary disease, the percentage in the group with suspected coronary disease being 20, and in the group with probable or certain coronary disease 30. The material has also been analysed in several other important aspects. Finally, various possibilities for improving this part of the coronary diagnosis are discussed.

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MYXŒDEMA WITH PERICARDIAL EFFUSION

BY

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There are few diseases that are so frequently mistaken in general practice as diseases of the thyroid gland. This not only applies to mild cases of thyrotoxicosis (Linnell, 1945) but also to cases of hypothyroidism and quite often even to fully developed cases of myxœdema with all its typical signs.

Just as in hyperthyroidism, in which the cardiac changes may be astonishingly small, there are instances of profound hypothyroidism with normal circulatory findings. Usually, however, the heart appears dilated to the right and to the left, and the cardiac sounds are muffled and soft. The term myxœdema heart has been applied to a condition found in about three-quarters of the cases of myxœdema (Zondek, 1918 and 1919; Fahr, 1925, 1927, and 1932; and Fournier, 1942). The myxœdema heart was described in the original report of Zondek (1918) in which he spoke of it as a clinical entity. Similar reports by Fahr, Fournier, and others, followed. Christian, and other observers, questioned the existence of such an entity and the cardiac signs were described as congestive heart failure complicating the myxœdema. It has, however, been proved that while digitalis is ineffective in those cases, treatment with adequate doses of thyroid is usually followed by a striking decrease of the size of the heart (reversible or " accordion heart "). Freeman (1934) and others found that at least part of the cardiac enlargement is due to pericardial effusion. White (1944) prints the picture of such a myxœdema heart in his text-book, showing a decrease of the transverse diameter of the heart shadow by 6 cm. as the result of successful treatment by thyroid. Considerable decrease in the size of the heart after thyroid treatment was further reported by Lehrman, Clark, and Means (1933) and by Campbell and Suzman (1934).

Cardiac involvement of a significant degree is an important sign, for it means that the grade of myxœdema is a serious one, or that other heart trouble, such as coronary or hypertensive disease, is present (White, 1944). Fahr (1925) found evidence of heart failure in 75 per cent of all his cases of myxœdema, 30 per cent of them showing rather severe signs and symptoms. While thyroid treatment relieved the signs and symptoms rather promptly, digitalis was found to be of doubtful value. He found many cases of myxœdema heart complicated by arteriosclerosis of the coronary vessels, and thyroid was found to be contra-indicated because the coronary flow may decrease at the same time as the power of the heart increases. The elevation of metabolism by thyroid therapy may induce symptoms of coronary insufficiency and attacks of angina pectoris may develop (White, 1944). In that case it is recommended to discontinue, or at least to reduce, the dosage of thyroid. According to White, congestive failure as a cause of death in myxœdema is very rare. The exact cause of the cardiac enlargement responsible for the term myxœdema heart is still a matter of dispute. It was thought to be the result partly of dilatation, partly of myxœdematous swelling and permeation of the myocardium by œdema, comparable to the alteration of the skin, and sometimes of an excess of fluid in the pericardium. While all these factors seem to play a role in the development of the myxœdema heart, recent observations seem to indicate that a pericardial effusion is generally present. Clear evidence of this was found in the case under discussion where a diagnostic paracentesis of the pericardial cavity revealed a pericardial effusion and 60 c.c. of straw-coloured fluid were aspirated. Similar results have lately been reported by a number of American observers but whether or not this effusion alone is responsible for all clinical signs is still uncertain. Tatum (1912) found pericardial effusion in thyroidectomised animals and Goldberg (1927) performed thyroidectomies on sheep and goats.

Two years later at autopsy he found the presence of pericardial effusion. The heart was pale and flabby and sections showed disintegration of heart muscle fibres.

Another interesting observation in myxœdema, and particularly in myxœdema heart with pericardial effusion, is the typical change of the cardiogram and the return of the tracing to normal after thyroid administration. In myxœdema the cardiogram is often characterized by an extremely low voltage curve. All the deflections are very small and inversion or absence of the T wave is not rarely found. Cutaneous alterations were at one time thought to be responsible for these changes. Recent investigations, however, tend to refute this assumption. Hallock (1933, 1934) found no abnormality in cardiograms of cases of generalized scleroderma and generalized ichthyosis. According to other observers the abnormal cardiogram and the cardiac enlargement of myxœdema results from myxœdematous swelling of the myocardial fibres. Adequate treatment with thyroid is usually followed by a striking improvement of the cardiogram. This too, was proved in the case under discussion. Since a reduction in the size of all waves of the cardiogram (low voltage) with occasionally inverted T wave in all leads is often found with effusion in the pericardial cavity, it may be difficult, if not impossible, to decide in a case of myxœdema heart whether the abnormal tracing is due to the myxœdema *per se*, or perhaps to a co-existing pericardial effusion. The alterations of the cardiogram in pericardial effusion are ascribed to the short circuiting of the action currents by the mantle of liquid which surrounds the heart so that only small potentials are intercepted at the surface of the body. The same alterations can be experimentally produced by the injection of normal salt solution into the pericardial cavity; such an artificial effusion can only be very small since a normal pericardium cannot be stretched. The low voltage tracing vanishes when the effusion is removed by therapeutic measures (Scherf and Boyd, 1945). To be sure the changes in the cardiogram in pericardial effusion are not invariably found, as in some cases the heart may not be entirely surrounded by fluid, and in some areas the heart may be adherent to the pericardium and to the surrounding tissues. An interesting cardiographic distinction between massive pericardial effusion and marked cardiac enlargement without effusion, has recently been suggested by Tung (1941): the duration of the electric systole (Q–T interval) is normal in the former and prolonged in the latter (White, 1944).

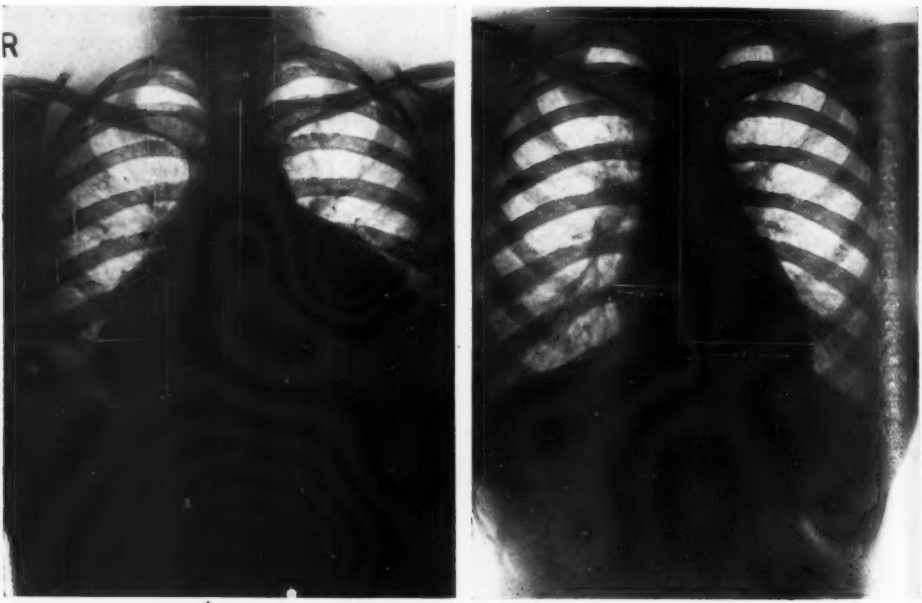

FIG. 1.—Teleradiograms of the heart before and after treatment.
(A) Before treatment, maximum transverse diameter 20·6 cm. (B) After treatment, maximum transverse diameter 12·0 cm.

Since no positive histological evidence proving the existence of a myxœdematous alteration of the myocardium has been obtained so far, the similarity of the cardiograms in pericardial effusion and in myxœdema could find its explanation in an abnormality common to both, that is, the effusion. It is therefore possible that a pericardial effusion existed in many, perhaps in all cases described under the term myxœdema heart.

Case Report

Miss A., aged 30 years, was admitted to hospital in January, 1945. For the last six months she had complained of dyspnœa on slight exertion, swelling of the ankles, puffiness of the face with swelling under the eyes, clumsiness of the hands, and loss of energy. She had put on a considerable amount of weight during the last few months and it was noticed that her speech became slow and slurred, although the patient herself was not aware of this.

On examination the temperature was subnormal, the respiration rate 20, and the weight 10 stone. Sallow pallor of skin which was dry and scaly, particularly on arms and legs, cyanosis over malar prominences, dry and brittle hair with some loss of outer third of eyebrows, puffy eyelids with narrow lid-slits, forehead slightly wrinkled, voice hoarse, speech slow and slurred, slow reactions, and slightly retarded cerebration. Cardiac dullness greatly increased to right and left. Cardiac impulse not visible. Apex beat displaced outwards and downwards, as judged by the intensity of the heart sounds, within the area of cardiac dullness. Heart sounds soft and distant, no thrill nor murmurs. Pulse 60 a minute, small, regular, and equal. Blood pressure 105/70. Abdomen rather prominent and flabby, but no evidence of fluid made out. Nothing abnormal palpable. No œdema.

The diagnosis of myxœdema with myxœdema heart was made.

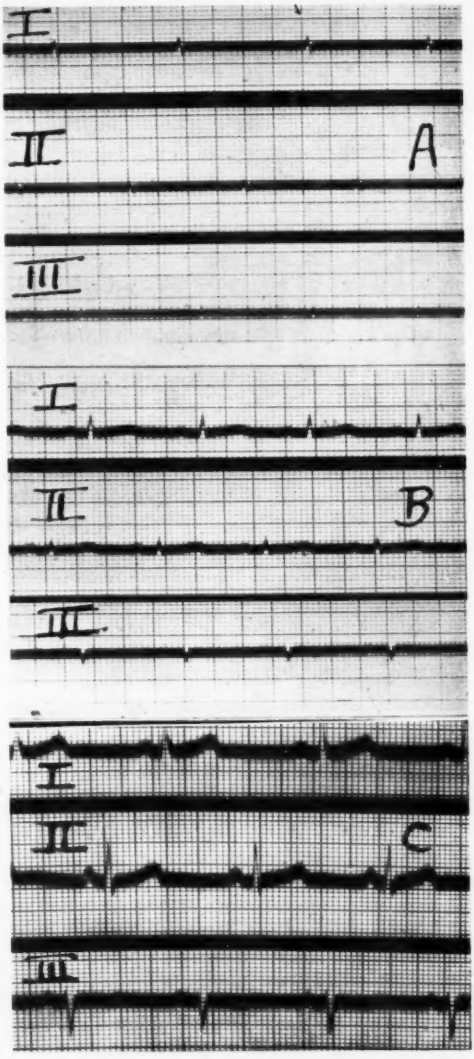

FIG. 2.—Electrocardiograms before and after treatment. (A) On admission, with extremely low voltage of all excursions. (B) After two months treatment with thyroid, showing increasing, but still low, voltage. (C) On discharge, showing return to normal, with left axis deviation.

X-Ray of heart on admission showed gross cardiac enlargement to the right and to the left, the maximum transverse diameter being 20·6 cm. (Fig. 1A). The electrocardiogram showed a low voltage curve and complete absence of P and T wave in all leads (Fig. 2A). Paracentesis of the pericardial cavity revealed the presence of a pericardial effusion. The needle was inserted in the fifth left intercostal space four and a half inches from the sternal border, and 60 c.c. of clear, straw-coloured fluid were aspirated. Plasma cholesterol 305 mg. per 100 c.c. Hæmoglobin 64 per cent. Red blood cells 3,230,000 per cub. mm. Colour index 0·98. White blood cells 5700 per cub. mm. Erythrocyte sedimentation rate 38 mm. in 1 hour (Westergren). Wassermann negative. The basal metabolic rate was not estimated

as no apparatus was available and the progress of the case was ascertained by monthly estimations of the plasma cholesterol.

Treatment and Progress. A trial dosage of thyroid, ½ grain b.i.d., was given for a week. It was then increased to 1 grain t.i.d., as no unfavourable reactions were observed. On this dosage the patient was kept for the next ten weeks when thyroid was reduced to ½ grain b.i.d. as a maintenance dose. She was also having fersolate tablets.

A series of radiograms of the heart showed a steady decrease in the size and the final one, after four and a half months of treatment with thyroid, showed a total decrease of the transverse diameter of the heart shadow by 8·6 cm. (Fig. 1B). The electrocardiogram became normal with all deflections well defined (Fig. 2 B and C), but there was now evidence of left ventricular preponderance. Blood pressure 120/85. Plasma cholesterol 185 mg. per 100 c.c. Hæmoglobin 94 per cent. Erythrocytes sedimentation rate 10 mm. in 1 hour. The raised erythrocyte sedimentation rate before treatment was probably due to the associated anæmia.

The patient was extremely fit on discharge, all the signs and symptoms of myxœdema had subsided, and she had lost 22 pounds within three months. She was advised to continue with the maintenance dose of ½ grain of thyroid, twice a day.

Summary and Conclusions

Some of the reported cases of pericardial effusion in myxœdema heart are reviewed, and the typical changes in the size of the heart and in the cardiogram are discussed.

A case of advanced myxœdema with gross enlargement of the heart in a woman of 30 years of age is recorded. Pericardial paracentesis revealed a pericardial effusion. The transverse diameter of the heart shadow before treatment was 20·6 cm. and after four and a half months of treatment with thyroid it decreased to 12 cm., showing a total decrease of 8·6 cm.

An initial low voltage curve of the cardiogram with absence of T wave in all limb leads was restored to normal after treatment, but there was evidence of left ventricular preponderance.

A trial dose of thyroid, ½ grain b.i.d., was given and as no unfavourable effect was observed this dose was increased to 1 grain t.i.d., and was finally reduced to ½ grain b.i.d. as the maintenance dose.

The similarity of the electrocardiograms in cases of pericardial effusion and in cases of myxœdema, suggests a common abnormality which may be the presence of fluid in both disorders. This would then support the opinion that a pericardial effusion exists in many, if not in all cases described as myxœdema heart.

We have to thank Dr. P. J. W. Mills, Medical Superintendent, for his kind permission to publish this case, and Dr. John Parkinson and Dr. J. W. Linnell for their interest and encouragement in the preparation of this paper. Our thanks are also due to Dr. Cornelius Papp for supplying us with some of the references, and to Dr. Cedric Hilliard, Radiologist, and his technical staff for their kind co-operation.

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ANGINA PECTORIS WITH ASSOCIATED LEFT PAROXYSMAL PTOSIS

BY

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The present case is reported because it presents what appears to be a unique combination of clinical phenomena.

An officer, 48 years of age, was well until August 1943. At this time, and at the end of a strenuous ten-day battle course, he was climbing a high wall when he had a sudden attack of severe pain in the chest accompanied by breathlessness. The pain did not radiate, but was generalized over the sternum and all the ribs on the left side anteriorly. He felt as though his chest was gripped in a vice and was very badly shaken, and stayed in bed for two days. A few days later he was " dressing down " one of his subordinates and at the same time vigorously demonstrating how a job should be done, when he suddenly felt an intense pain in the xiphisternum accompanied by severe dyspnoea. He had to stop talking and sit down at once and the pain slowly disappeared during the course of the next ninety minutes. At 3.30 the next morning he was awakened by a severe pain in the left arm, beginning in the elbow and spreading down the dorsum of the arm to all the knuckles; it was particularly acute in the thenar muscles. At the same time he became aware, though less insistently, of a mid-sternal pain, but on this occasion the arm pain was the more severe and was described as being like electric shocks passing down the forearm in rapid succession, rendering the hand practically powerless. He slept no more that morning but by breakfast time the pain was gone except for a dull ache in forearm and sternum. From this time until mid-December he had constant aching discomfort in the chest and left arm which turned to severe pain on moderate exertion. The continual pain in the arm was not well localized except that it was all below the elbow. Exertion, however, produced well-defined pain and tingling in the ulnar forearm and fingers, and if the exertion was continued the pain spread to the radial side of the hand and to the thenar muscles.

One day in October he was cycling uphill and already feeling rather breathless when he suddenly became aware that his left eye was running and that tears were streaming down his face on this side. He attributed this to the cold wind, and when he dismounted his bicycle, five minutes later, there was a burning pain on the left side of his face affecting chiefly the temple, eye, cheek, and angle of the lower jaw. At the same time he noticed that his left face felt warm and sticky. He lectured for nearly an hour in this condition and was then suddenly seized by a severe pain, which was mid-sternal and involved the whole of the left forearm and hand simultaneously. This was as severe as any attack he had ever suffered, but it disappeared after half an hour's rest and within an hour his eye had stopped running.

From this time on all the severe attacks began in the same way, with watering of the left eye followed by pain in the left face which was observed to be warm, congested, and moist to the touch. He noticed that if he sat down at the onset of lachrymation the subsequent chest pain was either much less severe or, on some occasions, did not come on at all; and that the onset of attacks with running of the left eye bore a constant relation to exertion, occurring always during the same hundred yards of his uphill journey from his place of work. If he exerted himself severely indoors the eyes watered in the same way, though, of course, he was

more commonly outside when this happened. When the exertion was violent and sudden, as in cycling up a steep hill against the wind, and particularly after lunch, the chest and arm pain sometimes occurred immediately, without lachrymation or facial pain, but on those occasions the latter symptoms began a few moments later and usually together.

He continued thus until mid-December. One afternoon just as he was recovering from an attack of post-prandial exertional pain he had his photograph taken. When the picture came back from the printers, he noticed that his left eye was practically closed. This was the first occasion on which ptosis was noted, and after this time he observed a gradual drooping of the left lid simultaneously with the onset of the other ocular symptoms in every attack. The ptosis was such that in a severe attack he could not see except by raising the lid manually.

In mid-December the constant chest and arm pain cleared, but he still had frequent exertional attacks of the same type and severity as before. They began with weeping and pain in the periphery of the left face and with flickering in the upper and lower lids, after which the upper lid began to droop. Usually about half an hour later pain began simultaneously in the chest and arm. This period was inversely proportional to the severity of the provoking exertion, and again, if this was severe and sudden, the related facial and ocular phenomena would follow the onset of angina. The eyelid remained down for the whole day following an attack, but on waking the next morning the lid was normal or showed only slightly ptosis; the same result often followed a short sleep even in the afternoon after an attack. Ptosis occurred with all severe attacks and he began to use it as a signal that, unless he rested, severe pain would certainly follow.

He never had any double vision or impairment of vision during these attacks, until on one occasion the day after a severe attack he noticed persistent diplopia on looking upwards. Sweating of the left side of the face during attacks became increasingly prominent.

When he inhaled amyl nitrite the chest and arm pain gradually disappeared over a period of time up to about fifteen minutes, depending on their severity. The pain in the face disappeared simultaneously, but the drug had no effect on the weeping or the ptosis, the former lasting for about half to one hour after the pain cleared and the ptosis until next day, or at any rate until after a period of sleep. Careful enquiry showed that the weeping and ptosis was always accompanied by mild mid-sternal discomfort and dyspnoea, and always followed by facial pain and then by chest and arm pain unless he rested absolutely at the onset.

The patient was admitted under our care on July 16, 1945, and has remained under observation for three months. Physical examination on admission showed an obese subject with a pulse rate ranging between 60 and 80 a minute and a regular rhythm. The brachial vessels were thickened, but the heart size and sounds were normal and no murmurs were heard. The chest and abdomen showed no signs of disease and the nervous system was intact. No cranial bruits were heard. The blood pressure was 140/80, and the urine showed no abnormal constituents. Radiological examination showed no evidence of cardiac or aortic enlargement and there was no peripheral arterial calcification. The Wasserman reaction was negative. Cardiography showed left axis deviation and steep inversion of T III.

Three attacks were observed before relief was obtained with vasodilators: in symptomatology they were identical with those described by the patient. The following observations were made during the half-hour preceding the onset of chest pain. The pulse rate showed no change but the blood pressure rose to 170/110. There was flushing of the whole of the left face with hyperhydrosis, extreme conjunctival congestion, left pupillo-dilatation with retention of normal pupillary reactions (evident only in a dim light and therefore sympatheticotonic), striking dilatation of the retinal veins on ophthalmoscopy, and left ptosis of moderate degree and gradual onset. Electrocardiography during an attack showed inversion of T II in addition to the previous findings. The facial and ocular symptoms cleared within an hour of relief of the pain by amyl nitrite inhalation, except that the ptosis remained: next morning the ptosis was still evident though less. After the second and severest attack it persisted for four days and was associated with vertical diplopia. At this stage he was seen by Squadron-Leader R. S. Sampson, ophthalmologist, who reported left ptosis and weakness of the left superior rectus muscle as revealed by red-green glasses and the Maddox rod test. At the same time conjunctival instillation of one drop of 1/1000 adrenalin, carried out at his suggestion, revealed left sympatheticotonia as shown by left pupillo-dilatation, the right pupil being unaffected.

Radiological examination of the skull, including stereoscopic views of the pituitary region and the sphenoidal fissures showed no deviations from normal and in particular no abnormal calcification or vascular shadows.

At present (10/10/45), after prolonged rest in bed, he is free from symptoms except for occasional post-prandial and exertional dyspnoea, usually preceded by left lachrymation and conjunctival suffusion.

Discussion

The phenomena described above as preceding and accompanying the patient's attacks of angina pectoris are not easy to explain. The features shown in the face and eye appear to comprise two clearly defined components. First, there is evidence of irritation of the cervical sympathetic in lachrymation, hyperhydrosis, vasodilatation, pupillo-dilatation, and abnormal pupillary response to adrenalin. Secondly, there is evidence of a partial paralytic lesion of the third cranial nerve, in ptosis and paresis of the superior rectus muscle, producing diplopia.

Wide irradiation of different impulses in the spinal cord might be related to the first group of symptoms, but would not explain the second. Of intermittent pressure from a dilated or aneurysmal vessel within the skull the reverse is true. Yet the constant association and close time-relation of the two components of the syndrome indicate the probability of an equally close relation in their mode of production.

Consideration of the anatomical pathways involved suggests a possible resolution of this difficulty. The nervous pathways of cardiac pain are not completely understood, but are considered to pass mainly via the sympathetic afferents of the cardiac plexus to the middle and inferior cervical (stellate) ganglia and the cervical sympathetic chain. From here they pass into the cord by way of the white rami communicantes and the upper four thoracic and possibly the eighth cervical posterior roots, to terminate at the base of the posterior horn in relation to the origin of the spino-thalamic tract.

The sympathetic pupillo-dilator fibres originate in cells of the posterior hypothalamic nuclei, having connections there with cortical levels, and they pass down through the medulla and cervical spinal cord in close relation with the pyramidal tracts, to terminate in the cilio-spinal centre, situated in the lateral horn of grey matter at the levels of the eighth cervical to the second thoracic segments. Here, preganglionic fibres originate, and, passing out with the lowest cervical and upper two thoracic anterior roots, make their way via the white rami communicantes to the inferior cervical (stellate) ganglia. These fibres course up the sympathetic chain to their cell-station in the superior cervical ganglia, where post-ganglionic fibres arise to be distributed to the eye by way of the coat of the internal carotid arteries and their branches. The sympathetic supply to the other parts concerned in Horner's syndrome—the tarsal muscles, the muscle of Muller, and the facial sweat glands and blood vessels—follow a similar, if less clearly defined, route.

These two pathways, the one afferent and the other efferent, therefore have part of their course (between the stellate ganglion and the spinal cord) in common, except that the bulk of the afferent fibres probably pass in the posterior, and the bulk of the efferent fibres in the anterior roots of the same segments. More significantly, their cell-stations within the spinal cord are in close proximity. The cilio-spinal centre lies in the lateral horn of the grey matter between the eighth cervical and second thoracic segments, with the related sympathetic efferent cell-stations close by, while the synaptic connections between the cardiac visceral afferents and the cells of origin of the spino-thalamic tract lie at the base of the posterior horns at the same levels of the cord.

These anatomical considerations suggest that the sympathetic symptoms in the present case are produced in the spinal cord. MacKenzie's hypothesis of segmental and extra-segmental sensory irradiation is used to explain the wide somatic reference of anginal pain, which in this case involved all dermatomes from the third cervical to the first thoracic, and it is perhaps significant that the facial pain in the present case also indicates a very widespread irradiation. The peripheral site of this pain, affecting chiefly the temple, cheek, and jaw, and sparing the nose and the central parts of the face, suggests a central origin and is consonant with excitation of the lower part of the sensory nucleus of the fifth nerve which extends

into the cord as far as the second cervical segment. It is known that referred cardiac pain may be accompanied by, and on occasion replaced by, sweating in the area of reference, while the salivation and polyuria that occasionally accompany angina pectoris can hardly be explained otherwise than as viscero-sensory reflexes similarly excited by irradiation from cardiac afferents.

In the present case, therefore, it is suggested that the sympatheticotonic phenomena were due to central irradiation within the spinal cord. The nature of the recurrent partial paresis of the oculo-motor nerve indicates a peripheral lesion, recoverable and probably involving only the superior ramus of the nerve that supplies the two muscles involved (levator palpebrae superioris and superior rectus). The delayed onset and slow recovery of the third nerve signs supports a mechanical causation, and we suggest that the paresis may have been due to local pressure on the superior ramus of the nerve by a dilated artery. The anterior site of the third nerve involvement, and the failure to elicit any evidence of impaired function in the first division of the fifth nerve on repeated testing during and between attacks, suggests that the ophthalmic artery or one of its branches rather than the internal carotid was responsible, and in its distension both the widespread sympathetic vasodilatation and the pre-anginal rise in blood pressure may have played a part.

Conclusions

A case of angina pectoris with two unusual groups of associated symptoms is described. In the first there was evidence of irritation of the cervical sympathetic, as shown by lachrymation, hyperhydrosis, vasodilatation, pupillo-dilatation, and an abnormal pupillary response to adrenalin. In the second there was evidence of a partial paralytic lesion of the third cranial nerve resulting in ptosis and paresis of the superior rectus muscle, producing diplopia.

The possible mechanisms have been discussed. It is suggested that the sympathetico-tonic phenomena are due to central irradiation within the spinal cord and that the recurrent partial paresis of the oculo-motor nerve may be due to local pressure on the superior ramus by a dilated opthalmic artery.

We wish to thank Squadron Leader R. S. Sampson for many helpful suggestions in relation to this case.

INDUCED CHANGES IN THE CIRCULATION IN CONSTRICTIVE PERICARDITIS

BY

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It is accepted that constrictive pericarditis curtails the normal excursion of the ventricles. This leads to a diminution in the output of the heart per beat, and, in spite of an elevated pulse rate, to a diminution also in the output of the heart per minute. Nearly all the studies of the circulation in patients with pericardial obstruction (Beck and Griswold, 1930; Burwell and Strayhorn, 1932; Beck and Cushing, 1934; Maltby, 1934; Burwell and Flickinger, 1935; Burwell and Blalock, 1938; Stewart, Heuer, Deitrick, Crane, Watson, and Wheeler, 1938) have been carried out under standard or basal conditions. The purpose of this paper is to place on record some additional measurements of the circulation under standard conditions, and also to report a series of studies of patients with constrictive pericarditis made under various special circumstances. These special studies include observations of the changes in the circulation associated with alterations in the blood volume, the pulse rate, and the venous pressure.

Presentation of Patients

The observations were made during the study and treatment of two patients, now to be described.

Case 1. G. M. was born in 1900. In April 1931 he developed right-sided pleurisy with effusion. His rather mild disability disappeared after removal of the fluid by tapping, and for several months he considered himself well. In November 1931 he was found to have a left-sided pleural effusion. There was fever, and active tuberculosis of the left apex was demonstrated by X-ray. At about this time he first noticed that his ankles were swollen and that he became short of breath in climbing a short flight of stairs. Under sanatorium care he improved. In 1932 he had another period of fever, this time associated with swelling of the abdomen, and he entered the Peter Bent Brigham Hospital. Here he was found to be a slight young man, a little pallid, but with a bluish tinge to the nail beds. The area of cardiac dulness was enlarged, the heart rate rapid, and the sounds distant. No murmurs were heard. The arterial blood pressure was 124/60. The abdomen was distended by ascites, and the liver was felt 3 cm. below the costal margin. The fluoroscope revealed the signs of apical fibrosis of both lungs and a considerably enlarged cardiac shadow said to be of water-bottle shape. The amplitude of the cardiac excursion was described as good.

Abdominal paracentesis removed 1800 c.c. of fluid in which tubercle bacilli were demonstrated by guinea-pig inoculation. As fluid slowly reaccumulated he complained of præcordial discomfort and a sense of drawing and tightness under the sternum which was worse on inspiration. After four months he had shown no improvement. The arterial pressure had declined to 98/64, the liver was larger, and the veins more distended. Fluoroscopic examination revealed the heart shadow to be no longer enlarged, and the amplitude of the cardiac excursion was now described as poor.

He went back to the sanatorium and after some months of rest in bed was much better. He was then permitted graded activity and in April 1934 was discharged.

From April 1934 until resection of the pericardium in 1938, his condition changed but little. He

was comfortable at rest but suffered dyspnœa and weakness on exertion, even such slight exertion as walking on the level at the usual pace. This severe limitation of exercise tolerance prevented him from performing the manual labour on which his livelihood depended.

Our own observations began in December 1935, and we have been in touch with him ever since. On any visit before the operation of 1938 he would display the following physical signs: the face was full and *suffused;* the feet and hands were cold to the touch and often clammy; there was a little cyanosis of the nail beds and an exaggerated longitudinal curvature of the nails. The neck veins were distended and firm and the venous pressure (see later) was always above the normal limits. The cardiac dulness was no longer as large as it had been, but measured only 4·5 cm. to the right and 6·5 cm. to the left. The dulness did not shift with change in the patient's position. The heart rate was more rapid than normal, the rhythm was regular, the sounds faint, and there were no murmurs nor additional heart sounds. The arterial pressure was 108/90 and there was slight paradoxical fluctuation. The lungs (in which there were changes consistent with healed fibrous tuberculosis) showed no moist rales. The vital capacity was moderately reduced (usually it was about 2400 c.c.). The liver was usually to be felt 3 or 4 cm. below the rib margin. Ascites was not present at this time.

It was apparent that we were dealing with constrictive pericarditis, the cause of which was tuberculosis and the result of which was an obstruction to blood flow of only moderate degree. (This will be shown clearly in the measurements reported later). Because his symptoms were mild and apparently non-progressive, operation was not then advised. Instead he was given graded exercise in an attempt to improve his general condition. He followed the regime faithfully but over the years seemed, if anything, to lose ground rather than to gain it. His limitations, although slight, were disabling, and in 1938 it was decided to advise treatment by operation.

On February 10, 1938, under avertin-ether anæsthesia, Dr. E. C. Cutler performed a pericardiolysis. At operation an interesting situation was found which was described in the operative note as follows: "When the pleura on the left was pushed aside it was noted that in the lower portion of the field there was a vigorous ventricular contraction while the upper portion of the field was motionless and muscular contraction was palpated as if through a thick sheet. The pericardium was opened and freed from the heart muscle down to the phrenic nerve on the left and to the right into a stiff area of diseased tissue. This area led into broken-down cheesy material quite characteristic of tuberculosis of the pericardium. Directly under the pericardium on the upper portion of the right ventricle lay a sheet of very hard fibrous tissue which limited the muscular movements beneath it. This *epicardial scar* was carefully shaved away and as it was removed there was marked improvement in the ventricular contraction, so much so that the muscle actually bulged into the field."

On microscopic examination the tissue removed was found to be dense hyalinized collagen with granulation tissue both old and recent. No tubercle bacilli were seen and no evidence of active tuberculosis was found. The pathologist's impression was that the tissue could be classified as healed tuberculous pericardium.

Almost immediately after the operation there was a change in the physical appearance of the patient. The suffused appearance of the face disappeared, the cyanosis of the nail beds was replaced by a normal pink colour, and the hands were no longer cold and clammy. At this time the venous pressure was within normal limits. After a fortnight, however, the pressure in the veins increased and it remained elevated for the next four months. During this time the patient experienced progressive gain in comfort though there was little laboratory evidence to suggest it. His ability to perform physical work improved, as did his sense of strength and well-being. Gradually, over months, his strength grew and his venous pressure fell. He became able to walk on the level without discomfort, climb hills or stairs without difficulty, and before long returned to his former occupation.

One more tuberculous chapter was written in his history in 1939 when he developed bone tuberculosis involving the right femur.

Since 1935 he has been under frequent observation in the laboratory. Many of the observations made there apply to the description of the course of his disease. They are reported in a subsequent section of this paper.

Case 2. (The course of this patient's illness has already been described by Burwell and Ayer (1941) in another connection; only a summary account will be presented here.) A. B. was a Lithuanian labourer of 54. In January 1938 he began to suffer from cough and coryza. A few weeks later he experienced dyspnœa on exertion, followed shortly by dyspnœa at rest, by orthopnœa, and by œdema of the ankles. When he entered the hospital on March 12, 1938, the heart rate was rapid, the rhythm regular, the pulse small. The heart was not enlarged and no murmurs were heard. The neck veins were visibly distended; the liver edge was 5 cm. below the rib margin; there were signs of fluid in both pleural cavities; and there was slight œdema of the ankles. A friction rub was audible over the præcordium and in the left axilla. The arterial blood pressure was 100/70 mm.; the venous blood pressure was 210 mm. of water. At fluoroscopic examination the excursion of the left heart border

was considered to be less than normal and there was *no* visible movement of the right border. An electrocardiogram showed low voltage, inverted T II and T III, and a normal lead IV.

Some improvement in comfort followed a few days of hospital care, during which time his chest was tapped and he received digitalis and mercurial diuretics. When he had lost some 16 pounds of fluid by various routes he could lie flat without dyspnœa and the vital capacity was found to be 3100 c.c., but the peripheral venous pressure remained elevated. The temperature rarely rose above 99° F. and was usually within limits considered normal.

A diagnosis of constrictive pericarditis was made. Tuberculosis was considered the cause of the pericarditis since the pleural fluid was found to contain tubercle bacilli by guinea-pig inoculation. Operation was advised. After nearly three months, during which time his disability continued and his venous pressure remained high, the patient decided to accept this advice. Dr. Cutler performed the operation in July 1938. He found a tough fibrous pericardium about 3 mm. thick closely applied to the heart. The entire anterior portion of this was excised and the heart was observed to pulsate more vigorously.

The venous pressure (Lyons, Kennedy, and Burwell, 1938) fluctuated somewhat during the first week after operation, but after that was never above 105 mm., i.e. it was well within normal limits. The evidences of congestion disappeared and it was considered that operation had relieved the mechanical obstruction to the entrance of blood into the heart. An account of his further course and of his tragic death from constrictive pleuritis a few weeks later has been recorded elsewhere (Burwell and Ayer, 1941).

These two patients, then, suffered from tuberculous pericarditis with constriction of the heart. Both had disability that was not extreme, and both were co-operative and interested participants in our studies of them. They were thus particularly suitable for the type of observation now to be described.

Methods of Study

Accepted methods were used for measuring various aspects of the circulation. The cardiac output was determined by the acetylene method, using the three-sample modification described by Gröllman, Friedman, Clark, and Harrison (1933). The venous pressure was measured by the direct method as applied by Lyons, Kennedy, and Burwell (1938). The blood volume was measured by the method of Gibson * and Evelyn (1938). Circulation time was the arm-to-tongue time indicated by the intravenous injection of 4–5 c.c. of sodium dehydrocholate.

Most of the observations on both patients were made while they were ambulatory. The patient would come to the laboratory in the fasting state, and after preliminary determinations of vital capacity he would rest in a reclining chair for 45 to 60 minutes before the estimation of the cardiac output was made. Following the determination of the cardiac output he was placed on an examining table for the measurement of venous pressure, circulation time, arterial blood pressure, and blood volume. When the patient did not have a determination of the cardiac output he rested on the examining table at least 15 minutes before the venous pressure was measured.

The observations made may be divided into two groups: those made under standard conditions before and after operation; and those made before, during, and after induced alterations in the circulation.

Observations Under Standard Conditions

Measurements of the venous pressure, blood volume, and cardiac output made under basal conditions before and after operation, are recorded in Table I and illustrated in Fig. 1 for Case 1, and recorded in Table II for Case 2. A persistently elevated venous pressure and a persistently low cardiac output per minute and per beat were present in both patients prior to operation. The blood volume in Case 1 was above the normal values. In Case 2 it was within the normal range based on height. It may be that the considerable emaciation and muscle atrophy in this patient affected the estimation of the normal values from his height or weight.

* We are indebted to Dr. J. G. Gibson II for his co-operation in making the measurements of the blood volume.

TABLE I

OBSERVATIONS ON CASE 1

Date	Venous blood pressure, mm. water	Total blood volume in c.c.	Heart rate per minute	Oxygen consumption per minute	A-V difference vol. O_2 per liter blood	Cardiac output liters per minute	Systolic output in c.c. per stroke	Blood flow in liters per sq. m. surface area	Vital capacity in c.c.	Circulation time in seconds	Arterial blood pressure, mm. Hg.
Normal values	Below 150	5400	64	231	59·0	3·87	60·4	2·21	4350	15–20	120/80
15/1/36	175	5870	81	242							
31/1/36	190		80	226							
28/2/36	175		80	210	61·1	3·44	43·0	1·99			
26/3/36	230		80	204	61·6	3·31	42·0	1·91	2350		112/80
2/4/36	180									39	
23/4/36	195									36	
21/5/36	202		70						2350	43	112/85
21/7/36	180								2500	35	114/74
16/12/36	217	6570	74	213	65·0	3·28	44·0	1·89		41	
2/3/37	211		80	221					2250	30	118/90
23/3/37			80						2500		
3/6/37			84						2200		108/82
22/7/37	230		76	215	65·0	3·30	43·4	1·93		44	104/76
5/8/37	223		72	201	66·0	3·00	44·6	1·72	2150		114/74
18/10/37	185								2500	30	
15/11/37	190	6125	72	218	65·0	3·36	46·6	1·93	2350	34	112/90
6/12/37	215										
15/1/38	195		72	211	68·7	3·07	40·4	1·74	2300	42	106/78
27/1/38	215	6560	74	229	68·5	3·34	45·1	1·94		42	
5/2/38	207		76							35	
10/2/38					Pericardiolysis						
15/2/38	115		80						1500	30	126/88
16/2/38	125								1650	30	112/70
18/2/38	125		80						1600	26	114/78
23/2/38	135	5400	90						1850	28	
26/2/38	150								1850	35	
1/3/38	140		80	203	55·7	3·64	45·5	2·26		32	
5/3/38	175		80	188	62·1	3·06	37·9	1·76	2100	30	110/82
9/3/38	170	5180							1900	28	
12/3/38	170		80	192	51·0	3·76	47·0	2·25	1900	45	112/82
15/3/38	210									50	
18/3/38	193	5910	76	198					2150	50	112/82
19/3/38			76	201	58·4	3·44	45·3	2·06			
31/3/38	185		76	211	66·8	3·16	41·5	1·93	2100	43	96/66
11/4/38	195		76	224	69·8	3·21	43·4	1·87		35	106/64
20/4/38	153									21	
26/4/38	190	6050	72	216	66·0	3·21	45·5	1·90	2200	25	
30/4/38	193		80							31	
16/5/38	155		72	251	65·9	3·81	54·4	2·22	2300	37	
27/5/38	170		70	210	59·8	3·51	50·2	2·03		39	
7/6/38	163		66	195	61·8	3·15	45·6	1·83	2400	40	
29/6/38	158	6040	72	210	68·6	3·06	42·5	1·79	2400	29	
21/9/38	125		72	208	68·0	3·06	42·5	1·79		32	
30/9/38	124	5650	66	205	67·0	3·06	46·0	1·79		22	
7/10/38	136		72						2550		11[illegible]70
1/2/39	115										
8/6/39	150	6040	66	203	59·5	3·41	51·6	1·98	2600	34	
30/3/40	110										
13/11/40	108	5300	70	196	51·5	3·83	53·2	2·06	2500		11[illegible]70
17/4/41	148		74	209	62·1	3·36	45·4	1·98			11[illegible]80
25/4/41	135		68								
26/5/42	125								2600	25	
24/4/43	135								2450	27	12[illegible]80
5/6/43			76	190	61·2	3·22	42·4	1·95			
5/4/44	126								2700		120/85

TABLE II

OBSERVATIONS ON CASE 2

Date	Venous blood pressure, mm. water	Total blood volume in c.c.	Heart rate per minute	Oxygen consumption per minute	A-V difference vol. O_2 per liter blood	Cardiac output liters per minute	Systolic output in c.c. per stroke	Blood flow in liters per sq. m. surface area	Vital capacity in c.c.	Circulation time in seconds	Arterial blood pressure, mm. Hg.
Normal values	150	5400	64	212	59·0	3·68	57·7	2·2	4250	15–20	120/80
21/3/38	255									19	100/70
28/3/38		5450	74	186	84·4	2·20	29·0	1·31	1800		
30/3/38	250		72	191	81·2	2·35	32·7	1·39		20	
1/4/38	237		72	197	84·9	2·32	32·2	1·37	1800	33	112/86
3/4/38					Digitalis stopped						
5/4/38	185*	5070*	70*	193*	78·5*	2·46*	34·6*	1·52*	1800*	26*	
12/4/38	232		72	175	74·0	2·35	32·7	1·42	1800	36	
14/4/38	245		76						1800	29	112/90
20/4/38			82	183	74·0	2·47	30·7	1·47			
21/4/38	213		78	176	74·0	2·40	30·6	1·46		18	
10/5/38	265†		100†	200†	78·0†	2·57†	25·7†	1·53†	1800†	33†	118/80†
24/5/38	205‡		88‡	163‡	62·0‡	2·64‡	30·0‡	1·57‡	2200‡	37‡	100/84‡
26/5/38	195§	4870§	88§	188§	74·0§	2·51§	27·9§	1·50§		38§	
14/6/38	208		88	189	84·0	2·24	26·0	1·33		39	
1/7/38	283‖		90‖							44‖	
8/7/38	265		88	197	75·0	2·63	30·0	1·56			
13/7/38					Pericardiolysis						
14/7/38	220		88								105/86
15/7/38	205		86								118/80
16/7/38	155		88								122/84
18/7/38	125		92								
20/7/38	110		94								130/90
28/7/38	122	4700									
8/8/38	150									18	
30/8/38	141									17	

* After mercupurin diuresis. † After high salt and unrestricted fluids.
‡ After 3 g. NH_4Cl daily and 2 mercupurin suppositories weekly.
§ After 2 c.c. mercupurin intravenously. ‖ Without diuretics or other drugs.

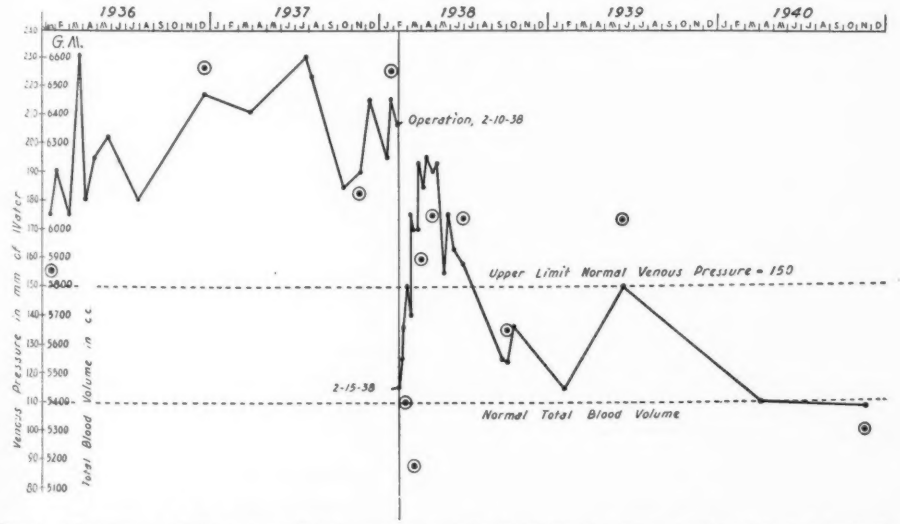

FIG. 1.—The course of the venous blood pressure and the total blood volume in Case 1 before and after pericardiolysis.

In both patients the venous pressure decreased after operation so that it was within the normal range. Of special interest was the *rise* in venous pressure two weeks after the pericardiolysis in Case 1. This rise persisted for several months; the venous pressure then returned to normal. In this patient there was relatively little improvement in the cardiac output following operation, though the output per beat was somewhat greater and the heart rate was slower. In Case 2 studies of the cardiac output could not be carried out after the operation because of the severe constrictive pleuritis which limited his breathing (Burwell and Ayer, 1941).

Several interesting spontaneous variations in the circulatory dynamics of these patients were encountered. First, a close relationship between the changes in the blood volume and the changes in the venous pressure was noted in Case 1. This is shown graphically in Fig. 2.

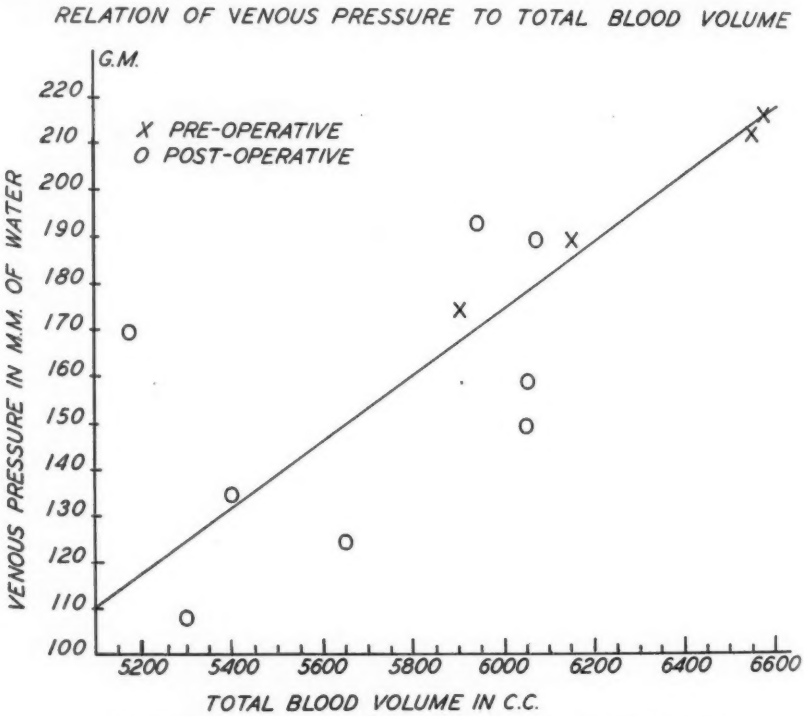

FIG. 2.—The relation of venous blood pressure to total blood volume in Case 1.

The relation may be expressed as: V.P. $= -239 +$ T.B.V. $(0{\cdot}069) \pm 18{\cdot}3$ mm. water. The correlation coefficient is $0{\cdot}83 \pm 0{\cdot}09$.

A similar relationship was apparent in Case 2, as seen in Table II. However, even with large spontaneous variations in venous pressure and blood volume no associated change was noted in the cardiac output per minute or per beat.

Second, there was considerable variation in the circulation time in both patients without corresponding change in the cardiac output or in the patients' general condition. In Case 1 a rough linear relationship was noted between the circulation time and the height of the venous pressure, as shown in Fig. 3. Case 2, who also had a high venous pressure and diminished cardiac output, usually had a prolonged circulation time but had several determinations within the normal range.

Third, when the heart rate increased there was a decrease in the output per beat in both patients. This was particularly evident in Case 2 who was completely digitalized at the start of his studies, and who showed a rise in heart rate when the digitalis was discontinued. The relationship between the heart rate and the output per beat is shown in Fig. 4. In his case,

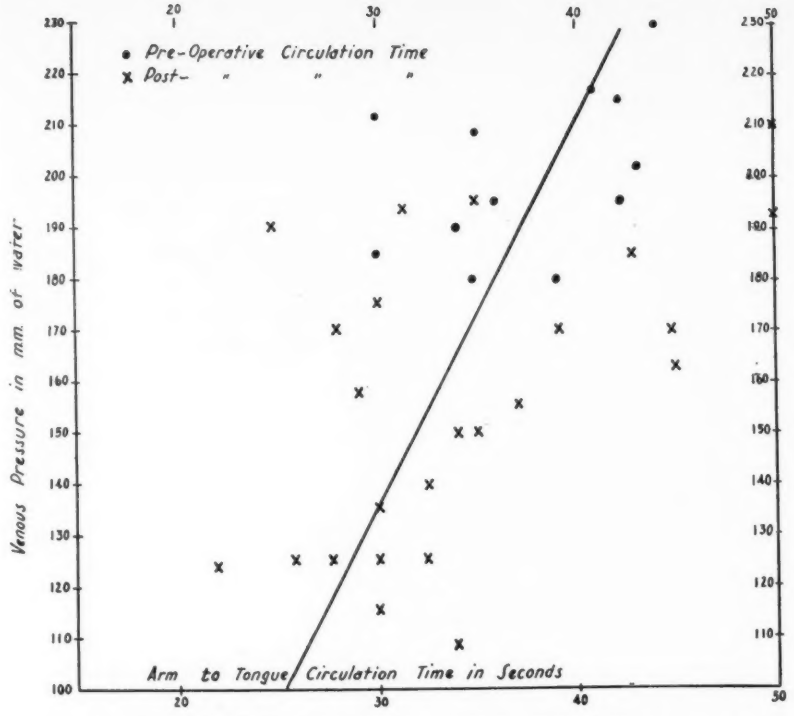

FIG. 3.—The relation of the circulation time and venous blood pressure in Case 1.

The relation could be expressed as: C.T.=11·86+V.P. (0·133)±5·8 sec. The correlation coefficient is 0·58±0·11.

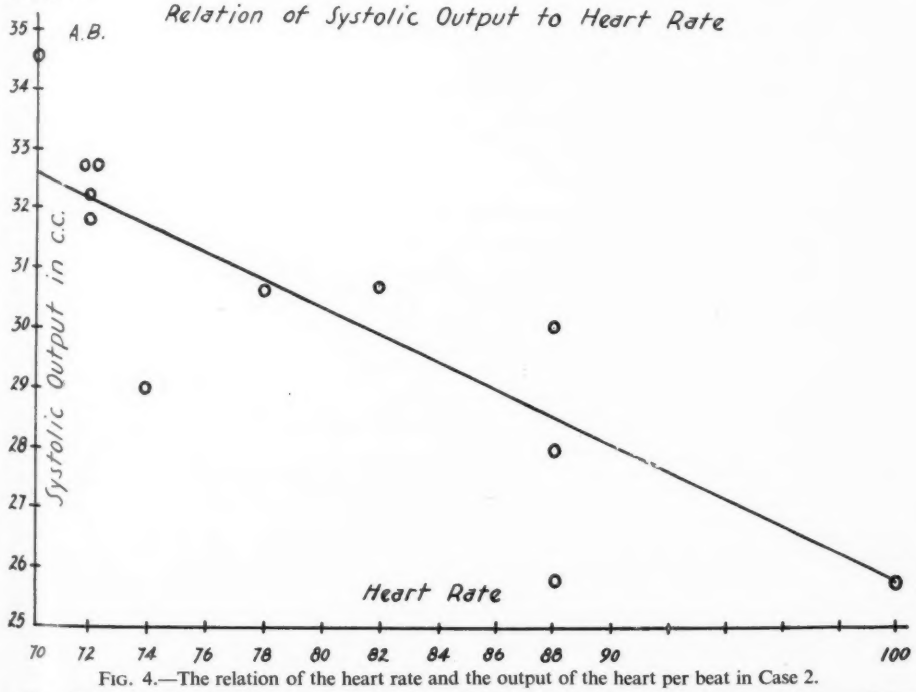

FIG. 4.—The relation of the heart rate and the output of the heart per beat in Case 2.

The relation may be expressed as: C.O./beat=49·1+heart rate (−0·235)±1·6. The correlation coefficient is 0·80±0·11.

even though there was a decrease in the output per beat, the output per minute showed a slight but progressive increase with the increased heart rate (Fig. 5). The same type of

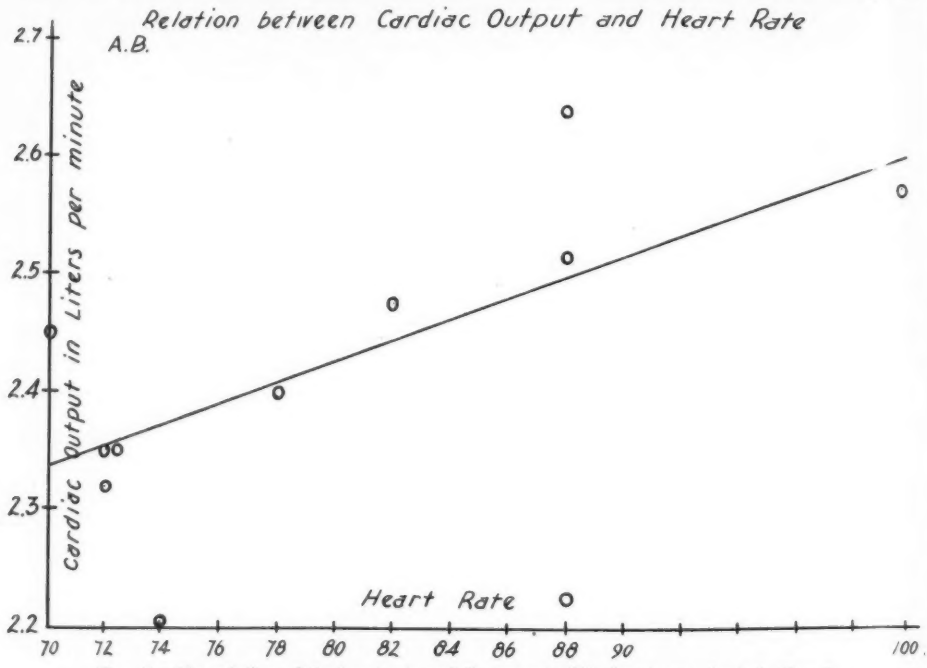

FIG. 5.—The relation of the heart rate and the output of the heart per minute in Case 2.

The relation may be expressed as: C.O./min. = 1717·6 + heart rate (8·78) ± 112·5. The correlation coefficient is 0·57 ± 0·2.

change was apparent in Case 1 but there was less variation in the heart rate and the changes were not so pronounced.

To amplify the observations made under standard conditions the following special studies have been carried out.

THE CHANGES IN THE CIRCULATION WITH CHANGES IN BLOOD VOLUME

It has been noted that there was a correlation between blood volume and venous pressure when spontaneous changes occurred. Such changes in blood volume and venous pressure were not reflected in alterations in heart rate or cardiac output. This observation led us to study the effect of rapidly induced changes in the blood volume.

After observing the effects of smaller amounts, 2900 c.c. of glucose and saline was administered by intravenous infusion in 45 minutes to Case 1. The results are recorded in Fig. 6. Although the venous pressure increased from 190 to 350 mm. of water there was no significant change in the cardiac output per minute or per beat. The heart rate increased only from 72 to 80. The circulation time was increased considerably at the middle of the infusion, and at the end of the infusion a 5 c.c. injection of sodium dehydrocholate failed to produce a reaction.

A similar infusion of 860 c.c. was administered to Case 2 in 15 minutes. There was a prompt increase in venous pressure from 185 to 325 mm. of water with the first portion of the infusion, followed by a gradual rise to 335 mm. with the last 150 c.c. In spite of a total rise of 150 mm. in the venous pressure there was no significant change in the cardiac output per minute. The output per beat fell from 34·6 to 29·7 c.c., while the heart rate increased from 70 to 76.

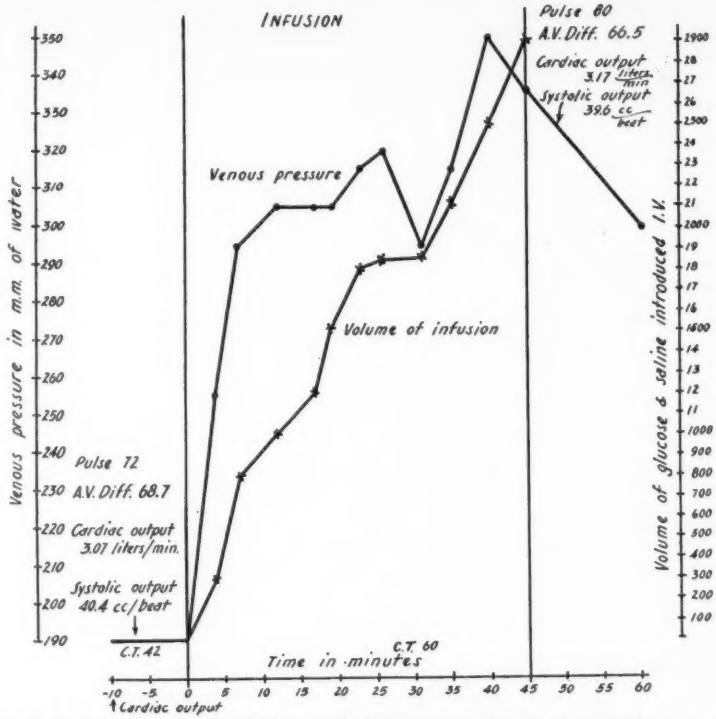

FIG. 6.—The effect of the intravenous infusion of fluid (5 per cent glucose in normal saline) on the venous pressure and on the output of the heart per minute and per beat, in Case 1.

Since a large increase in the venous pressure failed to alter the circulation significantly, the effect of induced decrease in venous pressure was then studied. After control measurements were made, blood (500 c.c.) was withdrawn over a twenty-minute period while the venous pressure, arterial pressure, and heart rate were observed. Immediately after the phlebotomy the cardiac output per minute and per beat were measured. The blood was then replaced and a third determination of the cardiac output made.

In Case 1 (see Fig. 7) there was a progressive fall in the venous pressure from 200 to 135 mm. of water during the removal of the first 300 c.c. of blood. The removal of an additional 200 c.c. lowered the venous pressure only 5 mm. further. The cardiac output per minute remained essentially unchanged. The heart rate changed from 72 to 76. The output per beat decreased only from 49·0 c.c. to 47·2 c.c. The replacement of the blood was associated with a slow but progressive rise in the venous pressure during the introduction of the first half of the infusion, and a more rapid rise toward the end until the venous pressure was 193 mm. of water. The patient, by this time, was somewhat disturbed by the long procedure. The oxygen consumption was elevated, the cardiac output was increased from 3·6 to 4·0 liters per minute, and the heart rate was 80. The circulation time remained essentially unchanged during the entire period.

A similar study of phlebotomy was made on Case 2 with generally similar results (Fig. 8). In this case, however, the venous pressure fell only 30 mm., from 215 to 185 mm. of water. As with Case 1 the venous pressure decreased during the removal of the first 300 c.c. of blood and it remained unchanged with the removal of an additional 200 c.c. The cardiac output per minute and per beat actually increased somewhat at the end of the phlebotomy which may represent a slight change from the basal state. With the re-infusion of the blood the venous pressure increased rapidly and progressively to 275 mm. The cardiac output, per minute and per beat, and the heart rate remained close to the initial determinations.

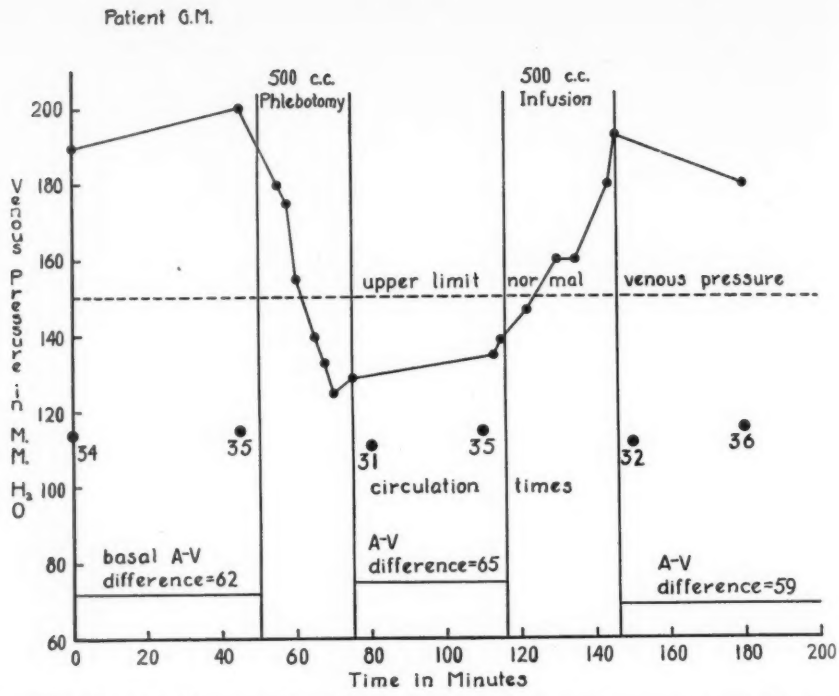

FIG. 7.—The effect of phlebotomy and re-infusion in Case 1 on the venous pressure, circulation time, and arterio-venous oxygen difference.

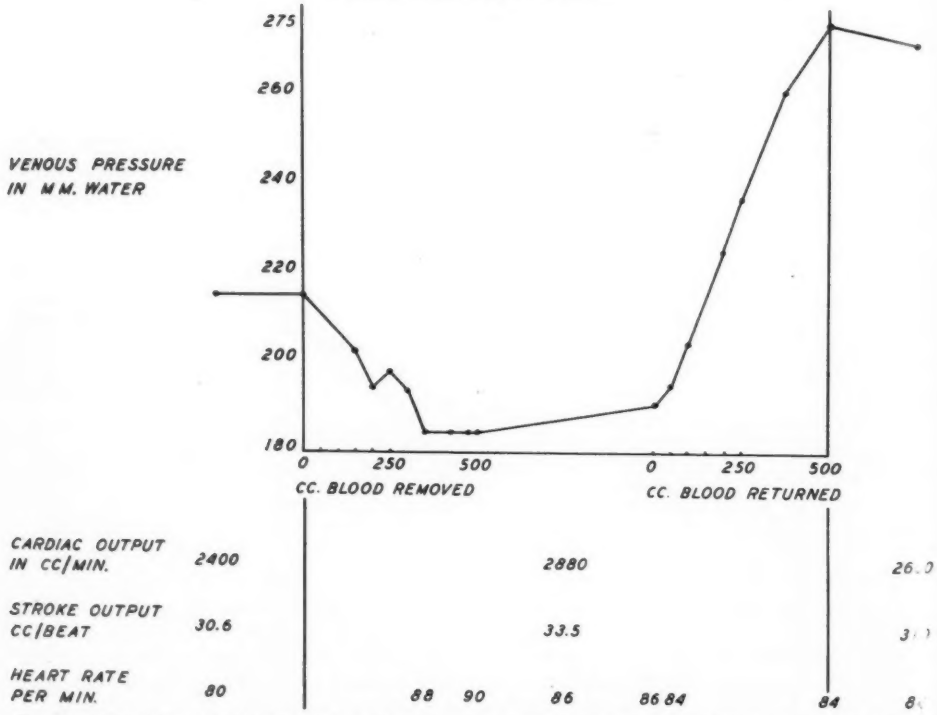

FIG. 8.—The effect of phlebotomy and re-infusion on the venous pressure, cardiac output per minute and per beat, and the heart rate in Case 2.

The Changes in the Circulation with Changes in Heart Rate

It was noted in the studies of spontaneous variation that when the heart rate was increased there was a decrease in the output of the heart per beat. In spite of this the cardiac output per minute was increased by such tachycardia, especially in Case 2. To test these observations further a transient tachycardia was produced by the intravenous injection of atropine sulphate so that comparable measurements of the circulation could be made immediately before and during the rapid heart action.

With Case 1 (Fig. 9), 3 mg. of atropine sulphate intravenously produced an increase in the

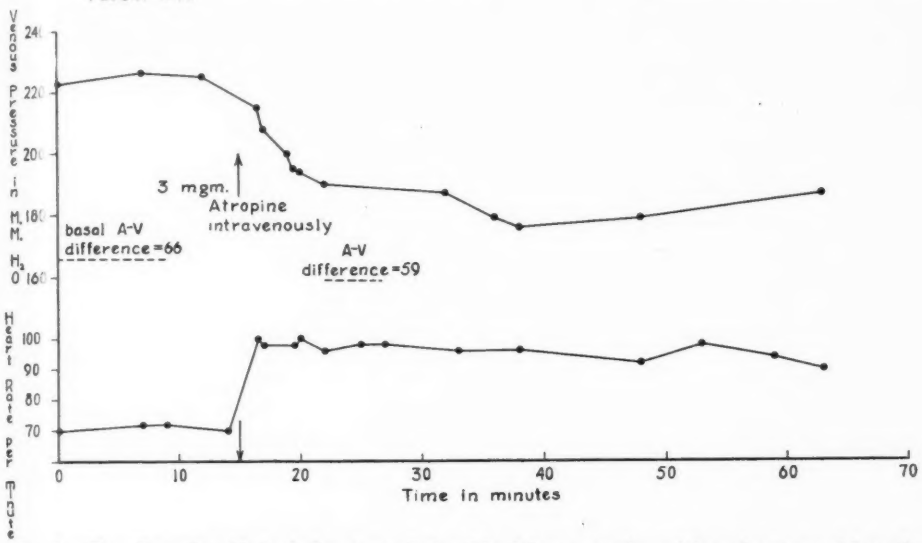

FIG. 9.—The effect of rapid rise in heart rate (induced by 3·0 mg. atropine sulphate intravenously) on the venous pressure and arterio-venous oxygen difference in Case 1.

heart rate from 70 to 98. With the onset of the tachycardia there was a fall in the venous pressure from 225 to 177 mm. of water, followed by a gradual return toward the control level as the tachycardia decreased. Although the output per beat decreased from 45 to 35 c.c., the output per minute was increased from 3·0 to 3·4 liters per minute. These observations were repeated a second time with essentially similar findings.

In Case 2, 4 mg. of atropine sulphate produced an increase in the heart rate from 72 to 94, and a fall in the venous pressure from 232 to 215 mm. of water. Although the output per beat decreased from 33 to 27 c.c., there was an increase in the output per minute from 2·35 to 2·7 liters. At the same time there was a slight increase in the vital capacity from 1800 to 2000 c.c., and a decrease in the circulation time from 36 to 26 seconds.

The effect of tachycardia that follows exercise was studied in Case 1. Immediately after a standard exercise the changes in the venous pressure and heart rate were observed. Fig. 10 is representative of the changes. There is considerable elevation of both venous pressure and heart rate at the end of exercise and both fall promptly with rest. The increased heart rate, however, continues for a considerable time, and is accompanied by a fall in venous pressure to a point below the initial resting level.

Discussion

It is accepted that the principal circulatory defect in constrictive pericarditis is limitation of diastolic filling of the ventricles. This results in a diminution of the output per beat. This is usually sufficiently severe to bring about a decrease in the cardiac output per minute even though a compensatory tachycardia may be present.

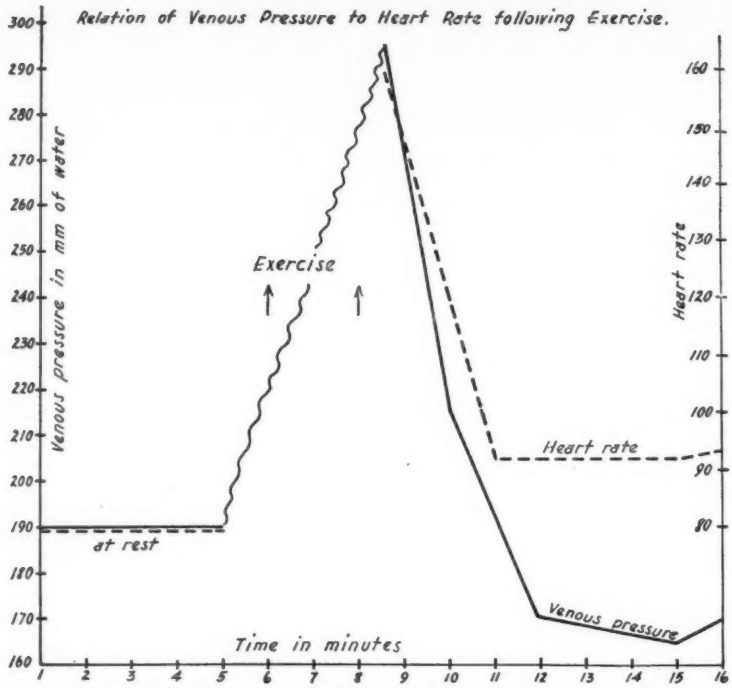

FIG. 10.—The effect of exercise on the venous pressure and heart rate of Case 1.

A question arises as to the effect of elevated venous pressure upon cardiac filling and cardiac output. When the heart is normal, a rise in venous pressure increases filling and output. What is the effect of such pressure change in the presence of pericardial obstruction? Where tamponade is due to pressure exerted by *fluid* in the pericardium (i.e. to a high intrapericardial pressure), an increase in venous pressure above some critical point may be expected to increase the flow of blood into the heart and so increase the cardiac output. This theoretical expectation is realized experimentally as is shown in a recent article by Cooper, Stead, and Warren (1944). Does the elevated venous pressure of constrictive pericarditis also assist in maintaining the circulation? It is apparent from our observations that large *spontaneous* variations of the venous pressure in these subjects have essentially no effect on ventricular filling as judged by alterations in the output per beat. *Induced* increases in the venous pressure of 160 and 150 mm. of water respectively, as a result of rapid infusion of glucose and saline, also failed to alter significantly the output per beat, the heart rate, or the output per minute. Rapidly induced decreases in the venous pressure of 60 and 30 mm. respectively also failed to affect the output per beat. That is, induced alterations in venous pressure over a total range of 220 and 180 mm. of water in these two patients did not influence the volume of the cardiac output. The conclusion that the high venous pressure of constrictive pericarditis is not effective compensation is in accord with expectation, since the obstruction to filling is not a high pressure (which may be overcome) but a non-distensible scar which puts a limit to dilatation of the ventricle during diastole.

It should be mentioned that while there was a progressive fall in the venous pressure of both patients during the first 300 c.c. of the phlebotomy, the further removal of 200 c.c. of blood failed to induce corresponding changes in the venous pressure. This sudden change in rate of fall in venous pressure during phlebotomy implies the operation of some compensatory mechanism. It may be that venous constriction occurs at that level and tends to prevent a further fall in the pressure.

The wide fluctuation in the venous pressure noted in following the course of those patients

appears to be related to changes in the volume of the blood and not directly related to changes in cardiac output. The elevation of the blood volume in these cases is similar in degree to that found in congestive heart failure and is probably due to similar mechanisms, one of which may be the abnormal retention of sodium. With such a retention of sodium either in normals (Lyons, Jacobson, and Avery, 1944) or in cardiacs, there is a resultant elevation of the blood volume and an increase in the venous pressure. The elevation of the venous pressure in Case 2 following the ingestion of large amounts of salt (Table II), and the fall in the venous pressure after ammonium chloride and mercupurin, suggest that the sodium balance may be an important factor in the control of venous pressure in such patients.

In most cases of constrictive pericarditis important manifestations are œdema, ascites, and pleural effusion. Presumably these result chiefly from the elevated venous pressure. These may be successfully influenced in the milder cases by a low sodium intake and occasional diuretics. In more severe cases the venous pressure cannot be lowered sufficiently to prevent the development of transudates, even with extensive diuresis.

The tachycardia noted in these subjects may well represent a mechanism tending to compensate for the diminished cardiac output per beat imposed by the limitation of diastolic filling. The increase in the cardiac output per minute and the decrease in venous pressure after induced tachycardia suggest that a rapid heart rate may be beneficial under these circumstances. Conversely a bradycardia may be injurious. Burwell and Strayhorn (1932) observed a patient in whom a decrease in the heart rate of 16 beats per minute, the result of digitalization, was associated with a fall in the cardiac output of 580 c.c. per minute. Similarly, in Case 2, the heart rate and cardiac output increased after digitalization was stopped. It is probable that digitalis has only an occasional place in the medical management of these patients with a regular rhythm, not only because of its effect on the heart rate, but also because it cannot alter the cardiac output through improvement in muscle tone since the heart is constricted rather than dilated. Exceptions to this rule may be found in patients with auricular fibrillation and many inefficient ventricular contractions, and in patients who have myocardial dilatation following relief of the constrictive pericarditis.

Increase in the heart rate is the only way in which these patients can increase the cardiac output (e.g. during exercise), since the associated elevation of the venous pressure fails to increase filling. The effect of tachycardia following exercise is similar to the effect of tachycardia produced by atropine in its ability to lower the venous pressure below the control level. This is not to say that an unlimited degree of tachycardia is desirable for these patients. There is probably an optimum rate in each individual, which is neither too high nor too low. Experience with patients having constrictive pericarditis *and* auricular fibrillation indicates that this optimum rate is considerably slower than the usual ventricular rate in uncontrolled auricular fibrillation.

Summary

Observations of the alterations in venous pressure, blood volume, heart rate, cardiac output per beat and per minute, circulation time, and vital capacity have been recorded for one patient with constrictive pericarditis who was studied for three years prior to pericardiolysis and for six years after the operation. Similar observations have been made on another patient with a more profound disability for a shorter time.

The spontaneous fluctuations in the venous pressure in these patients were not related to alterations in the cardiac output per minute or per beat, but appeared to be closely correlated with variations in the blood volume. It appears likely, therefore, that such fluctuations in venous pressure in these patients reflect changes in the water content of the body.

Increases in venous pressure of 160 and 130 mm. of water above the control level was produced in the two patients by the intravenous infusion of glucose and saline. These increases failed to alter the heart rate or the cardiac output per beat and per minute.

Decreases in the venous pressure of 60 to 30 mm. of water as a result of a 500 c.c. phlebotomy also failed to alter the cardiac output per minute and per beat.

Spontaneous increases in the heart rate were associated with decreases in the output per

beat, and with a slight net increase in the cardiac output per minute. Tachycardia produced by the intravenous injection of atropine sulphate was accompanied by an increase in the cardiac output per minute and a fall in the venous pressure. Tachycardia following exercise produced a similar decrease in the venous pressure below the resting level.

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PARAVERTEBRAL BLOCK AND THE ELECTROCARDIOGRAM IN ANGINA PECTORIS

BY

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Various surgical procedures in the region of the cervico-thoracic sympathetic system have been proposed for the treatment of angina pectoris. The paravertebral block of the upper thoracic sympathetic ganglia proved to be the most successful and the least dangerous. It was first introduced by Mandl (1925) who, using injections of novocain, reported that he had achieved relief of pain for many weeks. Swetlow (1926) recommended the use of alcohol and thought by this modification to prolong the effect of the paravertebral block. The sensory nerves of the heart and coronary vessels pass through the middle and inferior cardiac nerves to the middle and inferior cervical ganglia. Since there are no white rami communicantes between the cervical sympathetic chain and the spinal cord these sensory fibres must descend to the upper thoracic ganglia, from where they finally reach the spinal ganglia (Ranson and Billingsley, 1918, and Stohr, 1928). Besides the cervical cardiac nerves, there exist thoracic cardiac nerves which also serve as sensory pathways (Brauecker, 1927; Jonescu, 1927; and White *et al.*, 1933): these nerves pass directly through the posterior mediastinum to the upper four or five thoracic sympathetic ganglia. Thus, all the sensory pathways from the heart converge, uniting in the upper four or five thoracic ganglia. These anatomical facts explain the good results obtained by the paravertebral block of the upper thoracic ganglia (Marvin, 1935; Ochsner and DeBakey, 1937; and Levy and Moore, 1941).

Objections against any surgical intervention in the sympathetic nervous system as a method of treatment in angina pectoris have been raised by Danielopolu *et al.* (1931). They expressed the view that the sympathetics serve as vasodilators of the coronary vessels. Therefore, interruption of the sympathetic innervation may decrease the coronary flow and be even dangerous for a patient suffering from angina pectoris. Experimental studies on animals after ligation of the main coronary branches when the stellate ganglia or the thoracic ganglia have been removed do not, however, support this contention (Averbuck and Rachmilewitz, 1931; and White *et al.*, 1933). On the contrary, it has been reported that under these conditions there is a decrease in the mortality rate of the animals after ligation of the main branches of the coronary arteries (Leriche *et al.*, 1931).

The effect of the interruption of the sympathetic nerves on the coronary circulation in man is of special importance. Since in man coronary flow cannot be measured directly the use of the electrocardiograph affords the only method of revealing changes in the coronary circulation. The paper of Levy and Moore, who in 1941 reported their results in the treatment of cardiac pain by the paravertebral block contains also electrocardiographic observations. In 16 out of 45 patients cardiograms were taken and in 14 improvement was found. They assumed that the modification of the cardiogram indicated altering conditions in the coronary circulation.

The present investigation was carried out to study the effect of the paravertebral block on the electrocardiogram in cases of angina pectoris. A series of cardiograms was made in 12 patients treated by this method before and after the block. In 7 of them records were taken immediately before and twenty-four hours after the first injection to ascertain the

immediate effect of the block. All patients were suffering from severe anginal pain and were under medical observation for some time before they were subjected to this treatment. The treatment consisted of 4–7 paravertebral injections, the interval between each of them being three to six days. For the first injection novocain only was used while the following injections were performed with novocain and alcohol.* Eleven patients showed cardiographic changes before the block. Three of these did not show any improvement of the cardiogram after the block. In the first the cardiogram showed signs of bundle branch block, in the second signs of a recent myocardial infarction of the posterior wall, and in the third four negative T waves. In eight cases the cardiogram showed an improvement after the paravertebral block. The cardiographic changes in these cases were mainly concerned with the final deflection. Abnormalities of the T wave in at least two leads were present in all of them. The T waves were negative, iso-electric, diphasic, or flattened. In some cases there was also a depression of the S–T segment. After the paravertebral block the T waves became positive or more elevated and the S–T depression disappeared. In four cases this positive effect was observed already twenty-four hours after the block, but the maximum improvement of the electrocardiogram was generally obtained at the end of the treatment.

Table I gives an account of the cardiographic changes that took place as the result of the paravertebral block. The degree of elevation of the T waves following this treatment was designated as + corresponding to an elevation of 0·5 mm. ± 0·25 mm.; as ++ corresponding to an elevation of 1·0 mm. ± 0·25 mm.; and as +++ corresponding to an elevation of 1·5 mm. ± 0·25 mm.

TABLE I

Case No.	Sex and Age	Electrocardiogram	
		Before treatment	At the end of treatment
1	M. 46	S–T I and IV depressed, T I, T IV inverted	S–T I and IV iso-electric, T I upright ++, T IV upright +++
2	F. 48	T I, T IV iso-electric	T I upright +++
3	M. 51	T I iso-electric, T IV flat, P–R 0·25, QRS 0·13 sec.	T I upright ++, T IV upright ++
4	M. 57	S–T I depressed, T I inverted, T II, T IV flat	S–T I iso-electric, T I upright ++, T II upright ++, T IV upright +++
5	M. 51	S–T II depressed, T I inverted, T II, T III iso-electric	S–T II iso-electric, T I upright +, T II upright +
6	M. 44	T I flat, T IV inverted	T I upright, +, T IV iso-electric
7	M. 52	S–T I and II depressed, T I, T IV diphasic, T II flat	S–T I and II iso-electric, T I upright ++, T II upright +++,
8	M. 48	S–T I and II depressed, T I inverted, T II iso-electric	S–T I and II iso-electric, T I upright +, T II upright +

A few typical case histories are given.

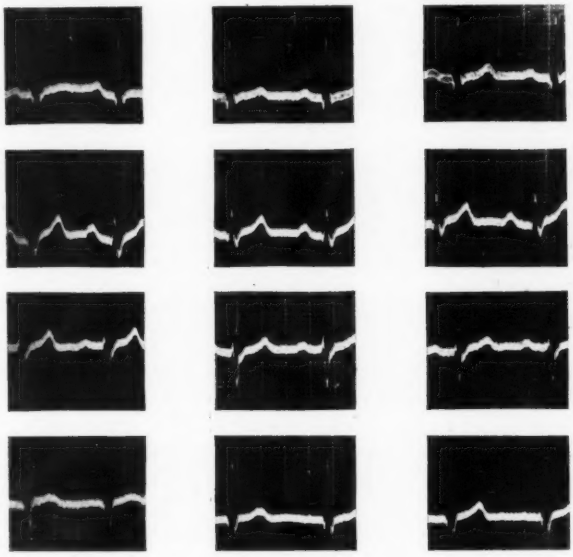
Case 3. J. A., aged 51, was admitted to the hospital on February 20, 1945. He was suffering for two years from attacks of pain in the præcordium with radiation to the left shoulder and arm. In the last seven months these attacks appeared very frequently, after the slightest effort and then even at rest, and therefore the patient was confined to bed for most of the time.

The clinical and X-ray examinations of the heart did not reveal any pathological findings apart from slight enlargement of the left ventricle. The blood pressure was 140/115. After ten days of observation, during which period the patient continued to suffer from anginal pain, the first paravertebral injection with novocain was done. Immediately after this procedure the pain subsided but appeared again a few days later. During one month five paravertebral injections with novocain and alcohol were performed. At the end of this period the pain disappeared.

A cardiogram done on the day before the paravertebral block showed left axis deviation, a prolonged P–R interval (0·27 sec.) and a slightly widened QRS in leads II and III. The T waves in the first lead were absent and in the fourth lead flat (Fig. 1A). Twenty-four hours after the first paravertebral injection the T wave in the first lead became positive (Fig. 1B). At the end of the treatment

* A detailed description of the technique is given in F. Mandl, *Paravertebral and Splanchnic Block*, Grune and Stratton, New York, 1945.

the T waves in the first and fourth lead became normal while no change took place in the prolonged P–R interval (Fig. 1C).



A B C

FIG. 1.—Case 3. (A) Iso-electric wave in lead I and flat T wave in lead IV. (B) Twenty-four hours after the paravertebral block; T I positive. (C) At the end of the treatment; elevation of T I and T IV. No change in the P–R interval and in QRS after the treatment.

Case 4. P. R., aged 57, was admitted on January 23, 1944. Two and a half months before admission the patient had had an attack of severe pain in the præcordium. Since then he was suffering from continuous pressure in this region. Every effort or emotion increased the pain; even the shortest talk and the intake of food could precipitate an attack. His blood pressure was 140/100. The X-ray of the heart was normal. The patient was observed for one week during which period aminophyllin and sedatives were given. In spite of complete rest and the medical treatment he continued to suffer from frequent attacks of angina pectoris. On February 1, the first paravertebral injection of the upper two thoracic ganglia was done. This resulted in a marked relief of pain. During a period of three weeks seven injections with novocain and alcohol in the upper four thoracic ganglia were performed. At the end of this period the patient was practically painless.

Two cardiograms were made before the paravertebral block was performed and both of them showed the same pathological changes. The T waves in the first lead were slightly negative and flat in the other leads (Fig. 2A). After the first paravertebral injection the T waves in the first lead became low, upright and higher in the other leads (Fig. 2B). At the end of the treatment the cardiogram was practically normal (Fig. 2C).

Case 6. J. F., aged 44, was admitted on September 3, 1944. Six months before admission, after an effort the patient experienced an acute sharp pain in the chest which continued for a few hours. This attack was accompanied by severe dyspnœa. Since then the patient was suffering from repeated attacks of anginal pain which appeared after walking and the slightest effort. He was sent to our department in July, 1944, but because of an intercurrent febrile disease a paravertebral block could not be performed at this time. During the course of the disease numerous cardiograms were taken and there was a suspicion that the first attack of pain was caused by a myocardial infarction (anterior wall). In the last month the cardiographic tracings showed identical changes. On clinical and X-ray examinations a slight dilatation of the left heart was found. The blood pressure was 140/90. The heart sounds were normal. The laboratory examinations did not show any pathological findings. On September 5, a paravertebral block with novocain was done. The first and second thoracic segments were injected. Shortly after the injection anæsthesia and paresis developed in the left arm and hand. Because of this complication the paravertebral block was not continued. The pain in

the chest disappeared completely after the injection, and while staying in the hospital for another month the patient did not feel any pain.

Immediately before the paravertebral block was performed a cardiogram was taken which showed left axis deviation, flat T waves in lead I, and inverted T waves in lead CF 4 (Fig. 3A). Twenty four hours after the paravertebral block the cardiogram showed a change. The T waves became higher,

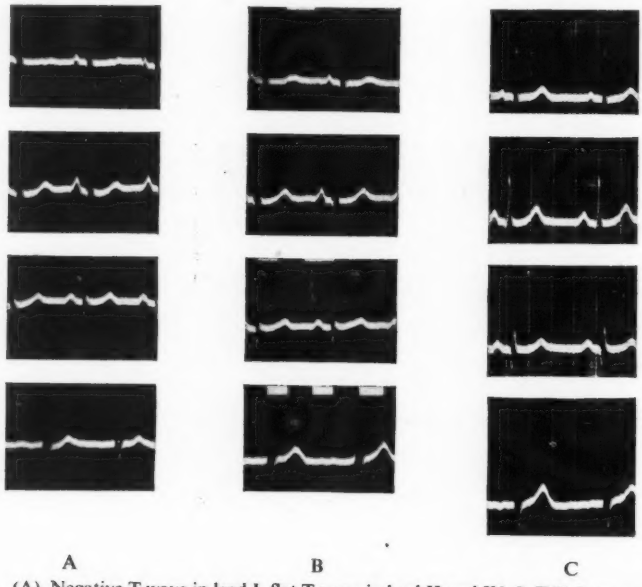


FIG. 2.—Case 4. (A) Negative T wave in lead I, flat T wave in lead II and IV, S–T II depressed. (B) Twenty-four hours after paravertebral block; T I positive, T II and T IV more elevated, S–T II iso-electric. (C) At the end of the treatment, the cardiogram shows further improvement and is practically normal.

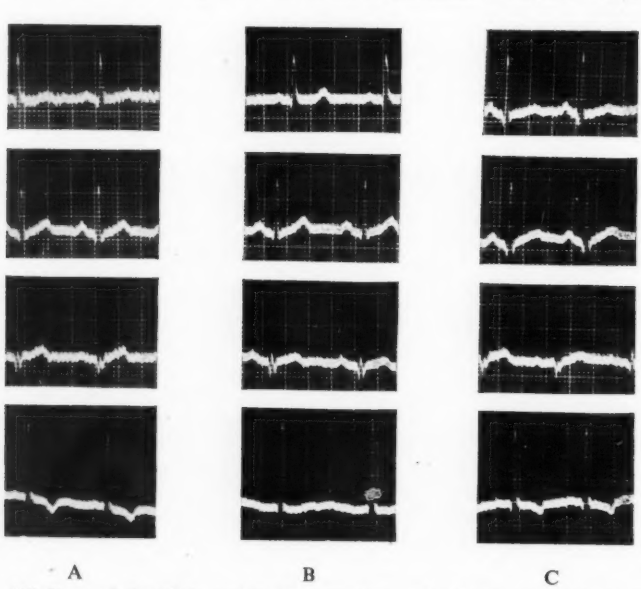


FIG. 3.—Case 6. (A) T wave in lead I flat and in CF 4 negative. (B) After novocain block; T I more elevated, T IV iso-electric. (C) Twenty-four hours later, the cardiogram shows the same changes as before treatment. The improvement was only temporary.

upright in the first lead and iso-electric in the fourth lead (Fig. 3B). One day later the cardiogram showed the same pathological changes as before the paravertebral injection (Fig. 3C). The improvement was only temporary, and two days after the paravertebral injection the cardiogram showed the same changes as before the treatment.

COMMENT

The electrocardiographic changes found in our cases before treatment were concerned especially with the T waves, alterations that are generally believed to be caused by anoxæmia of the myocardium due to a diminished coronary flow. The most frequent causes of a diminished coronary flow are arteriosclerosis and spasm of the coronary vessels. Anoxæmia is according to the present concept the chief cause of cardiac pain (Keefer and Resnik, 1918; Sutton and Lueth, 1930; Rothschild and Kissin, 1933; and Levy *et al.*, 1938). While the relief of pain achieved by the paravertebral block can be explained by the interruption of the sensory pathways, the improvement of the cardiogram is most probably produced by an increased coronary blood flow and a greater oxygen supply to the heart muscle. The mechanism by which the improvement of the coronary circulation is achieved deserves special comment. It is agreed that the vasoconstriction of the peripheral vessels is mediated by the sympathetic nerves. But there is a discrepancy of opinion regarding the innervation of the coronary arteries. Leriche *et al.* (1931) assumed that the innervation of the coronary vessels follows the general law of vasomotor innervation and thought to have proved it by experiments in dogs: they ligated the descending branch of the left coronary artery at various levels and found that after ligation at higher levels the animals died from ventricular fibrillation, while after removal of both stellate ganglia the animals survived. Katz and Jochim (1939) found that cutting the sympathetic supply to the heart usually produced a coronary vasodilatation, sometimes, however, a vasoconstriction was noted; they concluded that the stellate ganglia send to the heart adrenergic coronary dilator and adrenergic coronary constrictor fibres. Evidence has also been accumulated indicating that the innervation of the coronary arteries is different from that of the systemic vessels. Anrep and Segall (1926) first showed that the vasoconstrictor fibres are carried chiefly in the vagus while the sympathetic nerves contain the vasodilator fibres. A series of investigations by improved methods confirmed these findings (Green *et al.*, 1942; Essex *et al.*, 1943). Recently also Gregg and Shipley (1944) showed that stimulation of the stellate ganglia and their cardiac branches causes an increase in the coronary blood flow.

The clinical experience with paravertebral block as a method of relieving pain in angina pectoris and our observations indicate that the blocking of the upper thoracic sympathetic ganglia may cause an improvement of the coronary circulation. The change of the cardiogram following this procedure furnishes objective evidence for the beneficial effect on the coronary blood flow. The improved circulation may be a direct sequel of the blocking of the sympathetic or the relief of pain may cause an abolition of reflex spasm in anatomically unaffected vessels and thus a dilatation of coronary vessels; this last possibility was assumed by Levy and Moore (1941). In our series of cases there was not always a parallelism between the improvement of the cardiogram and the persistence and severity of cardiac pain. In one of our patients (Case 6) a block with novocain of the upper two thoracic ganglia only was performed: in this case there was an improvement of the cardiogram for twenty-four hours; but afterwards it showed the same changes as before treatment although the patient was relieved from his cardiac pain for several months. In other cases the cardiogram remained improved many months after the paravertebral block although the patients suffered again from attacks of angina pectoria.

In the three cases in which no improvement of the cardiogram after the treatment was observed, the cardiogram showed marked pathological changes (bundle branch block, myocardial infarction, and inverted T waves in four leads). It may be assumed that in these cases the changes in the cardiogram were caused by severe anatomical alterations in the coronary vessels and therefore no improvement could take place.

Summary

In twelve patients suffering from frequent attacks of angina pectoris the electrocardiogram was studied before and shortly after the paravertebral sympathetic block. Out of eleven cases with cardiographic abnormalities before the block, eight showed an improvement of the cardiogram. The T waves which before the block were flat, diphasic, iso-electric, or negative showed a tendency to return to normal. The improvement of the cardiogram did not always coincide with the relief of pain.

We take the opportunity of thanking Prof. F. Mandl and Dr. H. Melwidski, who performed the paravertebral injections.

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